Prevention of cardiovascular morbidity in HD patients:

The role of dialysis techniques

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Specific cardiovascular risk factors in HD patients

- Fluid overload - hypertension, LVH, heart failure
- Hyperphosphatemia - vascular calcification, arterial stiffness
- Inflammation - atherosclerosis
- Increased $ß_2$-microglobulin (and other MMW solutes)
- Lipid disturbances
- Anemia
- Hemodynamic instability (intradialytic hypotension)

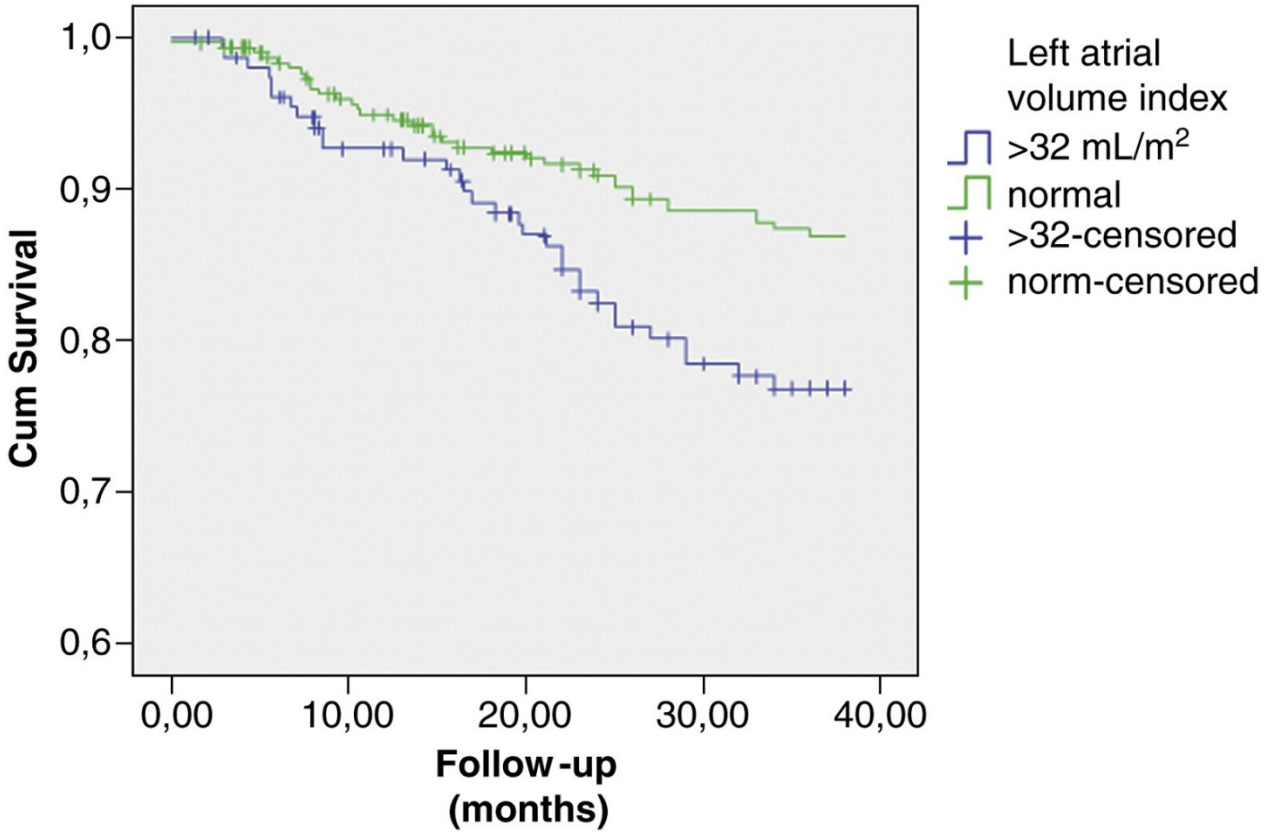
How to improve cardiovascular outcomes in HD patients

- VOLUME CONTROL
- MORE DIALYSIS (Longer and/or more frequent)
- HIGH FLUX DIALYSER & ULTRA-PURE DIALYSATE
- HEMODIAFILTRATION
- TO MANIPULATE DIALYSATE CONTENT

VOLUME CONTROL

Overhydration and mortality in HD patients

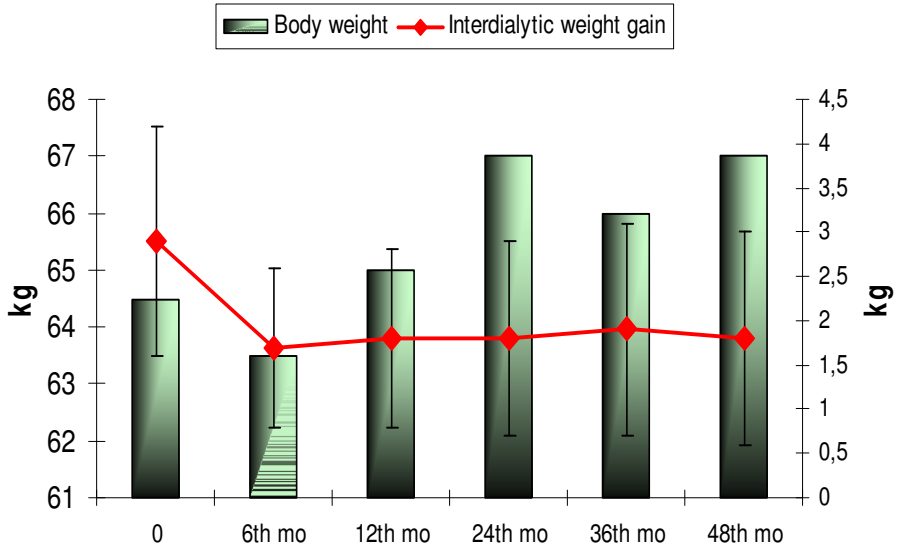
- 555 HD patients
- Echocardiography
- 3 years follow-up

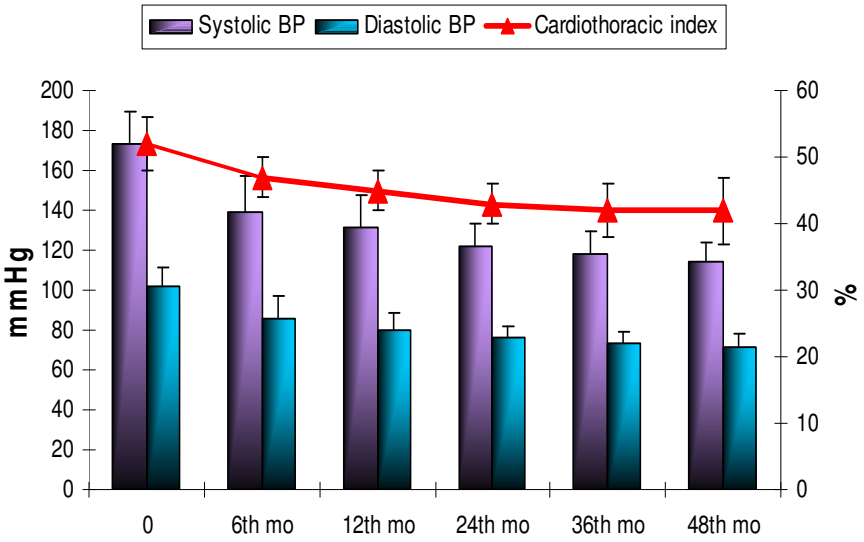


- Left atrial diameter and interdialytic weight gain independent predictors of mortality

Ozdogan O, Am Heart J 2010; 159: 1089

The results of switch from conventional approach to volume control strategy



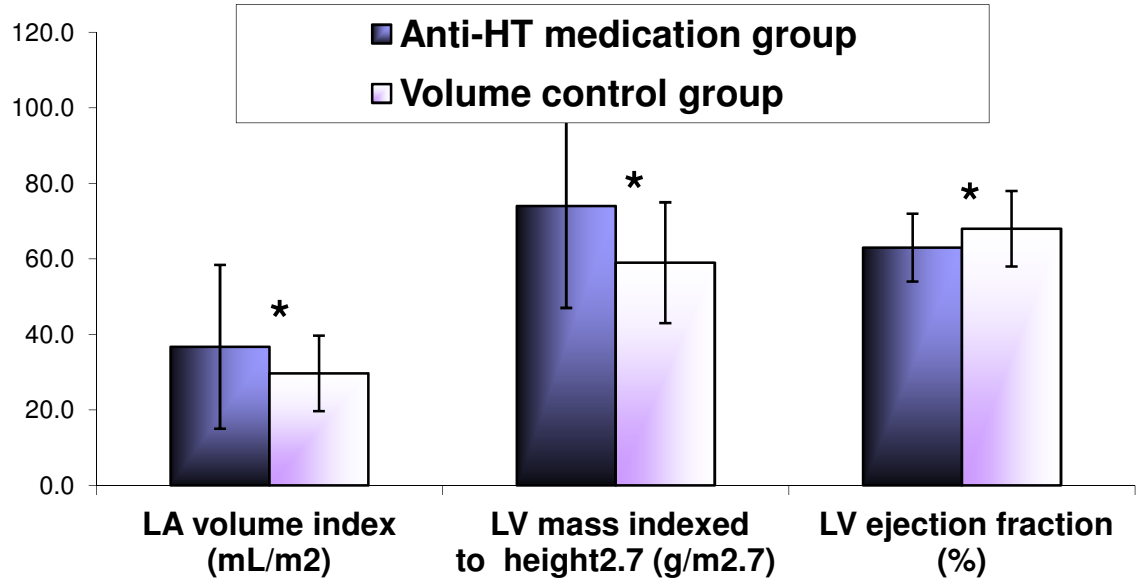


- **67 hypertensive HD patients**, stop anti-hypertensive medications, insistent UF, dietary salt restriction; **4 years follow-up**
- At the end, only 4% in need of anti-HT medication
- No edema, no heart failure
- Intradialytic hypotension and cramps decreased

Ozkahya M, Am J Kidney Dis 1999

Volume control strategy versus conventional approach

- Comparison of the two dialysis centers regarding BP and cardiac geometry and functions (Center A practiced volume control strategy, Center B anti-hypertensive medication - based strategy)



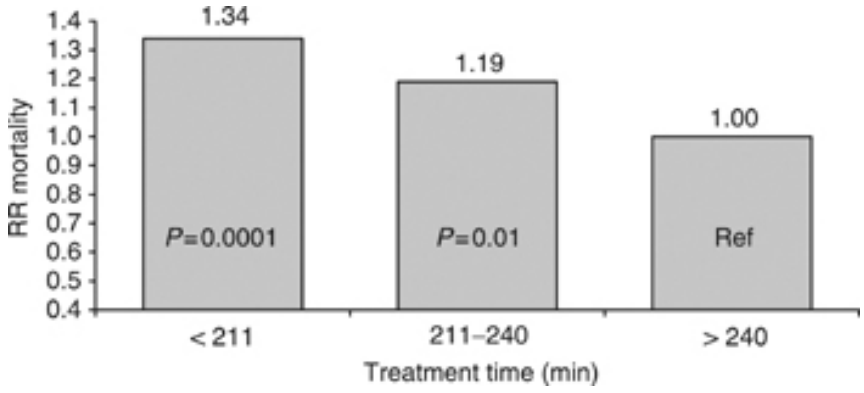
* p<0.001

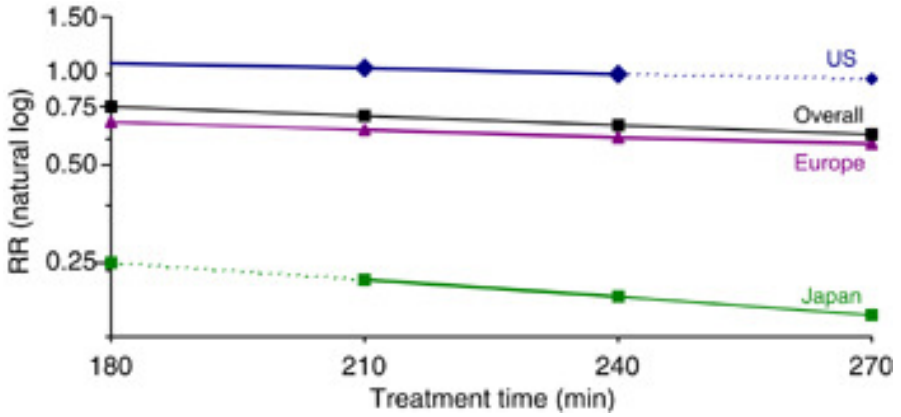
- Despite similar BP control, volume control strategy is associated with lesser cardiac dilatation, lower left ventricular mass and better preserved systolic and diastolic functions

Kayikcioglu M, Nephrol Dial Transplant 2009

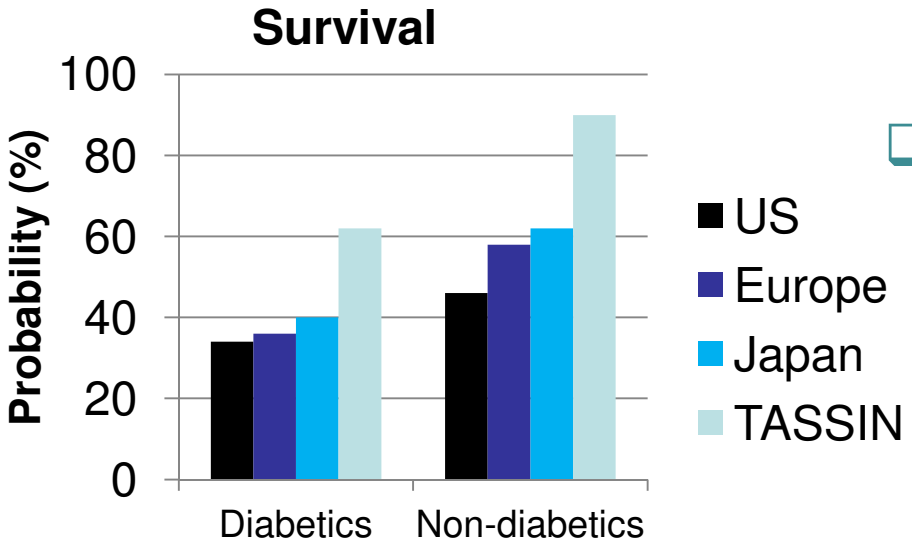
MORE DIALYSIS

Duration of HD sessions





- Duration of HD session is essentially important in everywhere



- Best survival data from Tassin with three times 8-h dialysis

Saran R, Kidney Int 2006; 69: 1222

Charra B, Kidney Int 1992; 41:1286.

8-h versus 4-h three times weekly HD

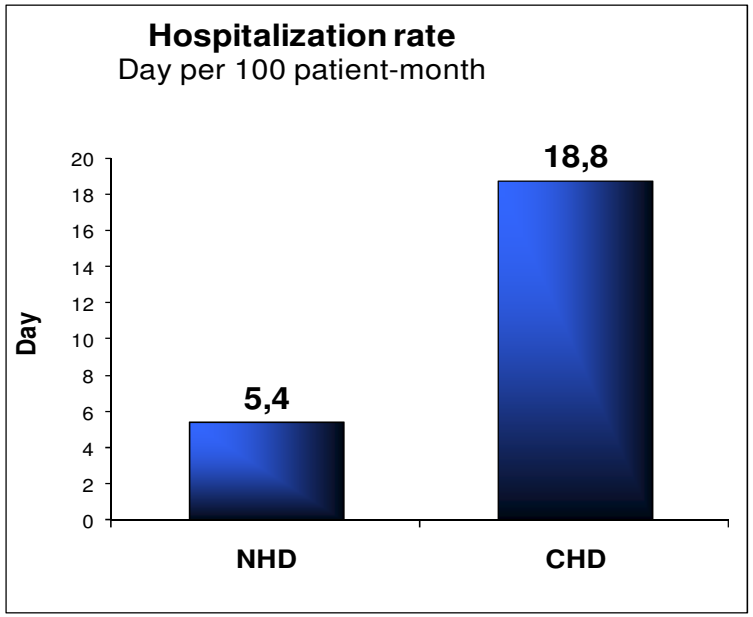
- Prospective, case-controlled study, 247 prevalent HD pts to in-center NHD, 247 age-, sex-, diabetic status-, HD vintage-matched pts CHD, 12 months

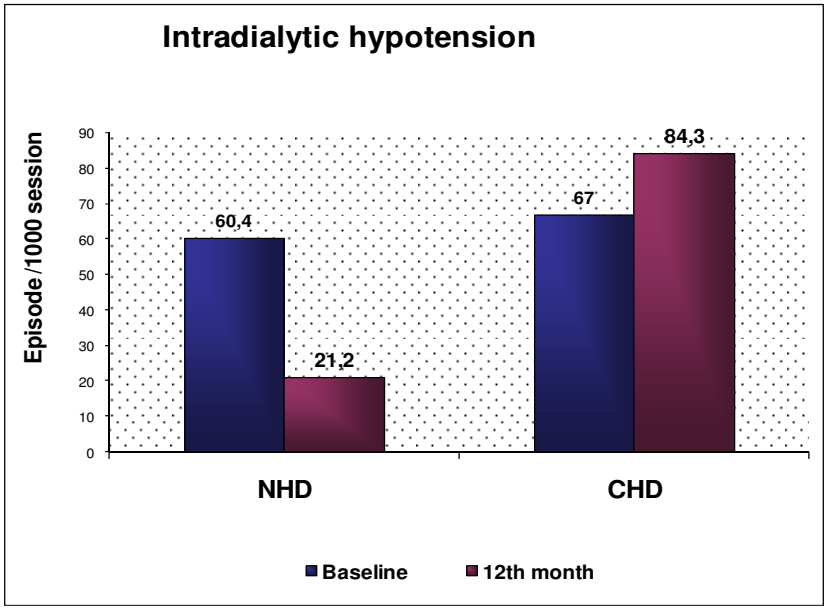
	NHD N=247	**CHD** N=247	p value
Albumin (g/dl)	4.02 ± 0.24	3.94 ± 0.29	0.001
Hemoglobin (g/dl)	11.8 ± 1.4	11.4 ± 1.6	0.02
Phosphate (mg/dl)	3.87 ± 1.20	4.96 ± 1.14	<0.001
Death rate (n/100-pt-yr)	1.77	6.23	0.01

- **NHD ⟶ Higher albumin and Hb , lower PO_4 and mortality**

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

Effect of longer HD on hospitalization and intradialytic hypotension

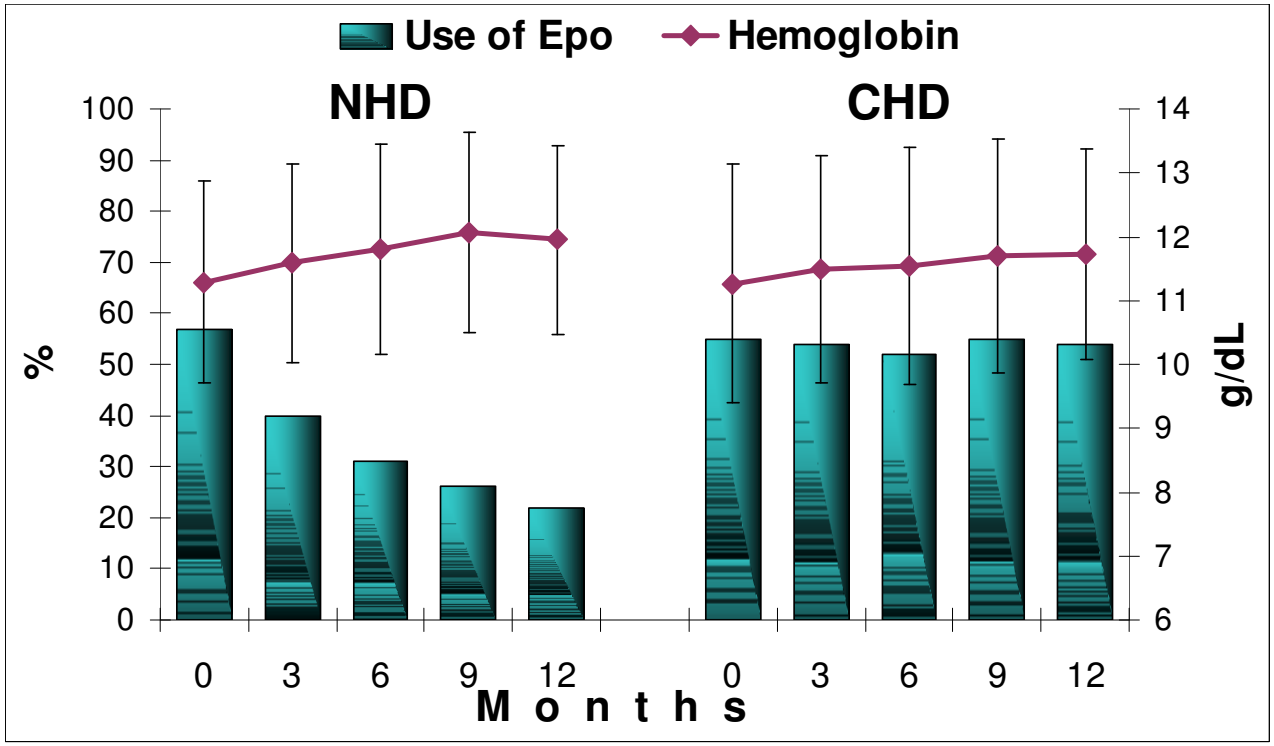




- 73% less all-cause hospitalization rate in the NHD arm ($p<0.05$)
- Marked decrease in intradialytic hypotension episodes in the NHD group ($p <0.001$)

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

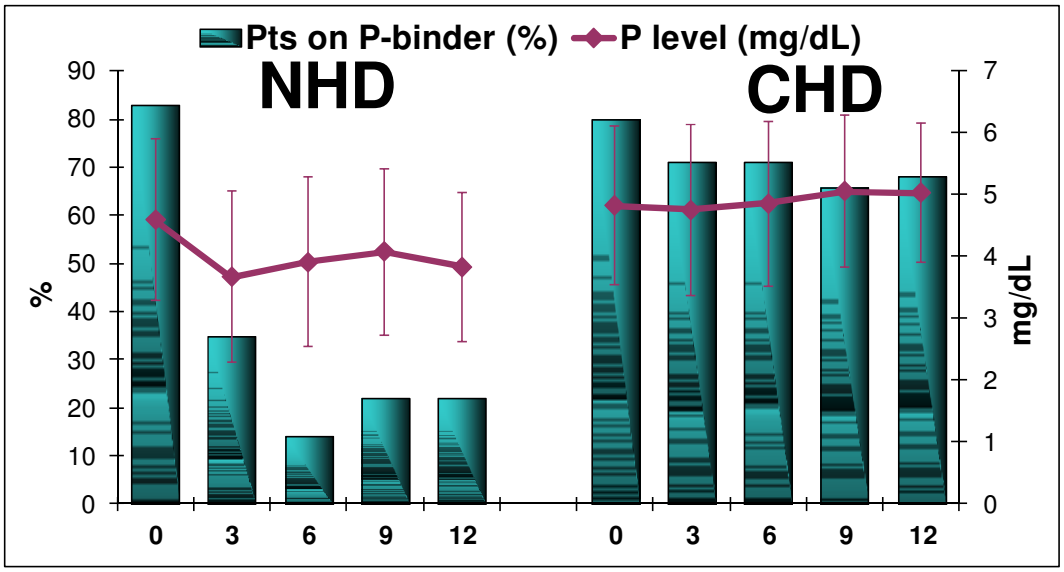
Effect of longer HD on anemia management



- Hemoglobin levels slightly increased in both arms ($p<0.01$)
- Proportion of patients on Epo declined from 55.5 to 24.7% in the NHD group ($p<0.001$)

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

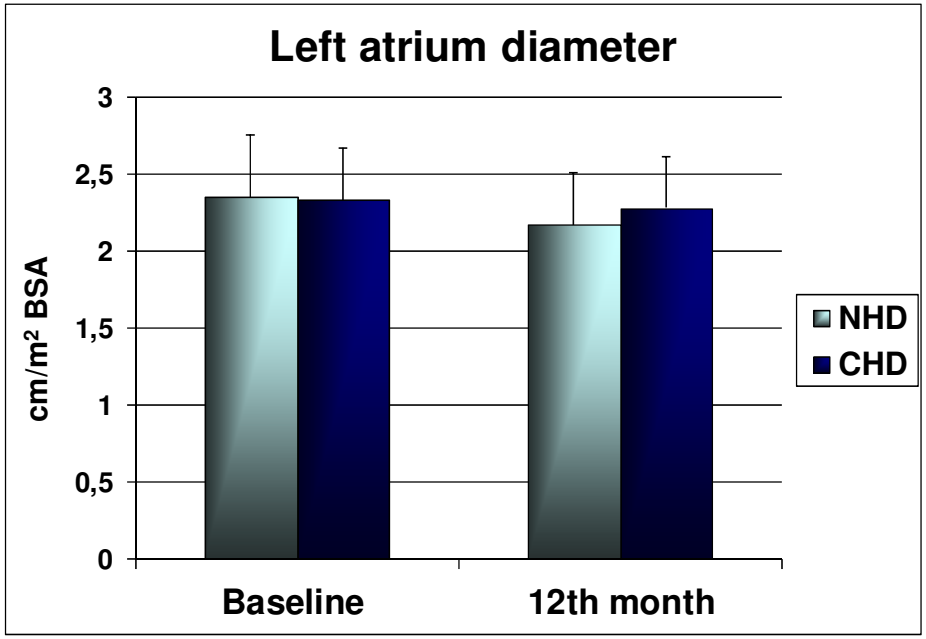
Effect of longer HD on phosphate control

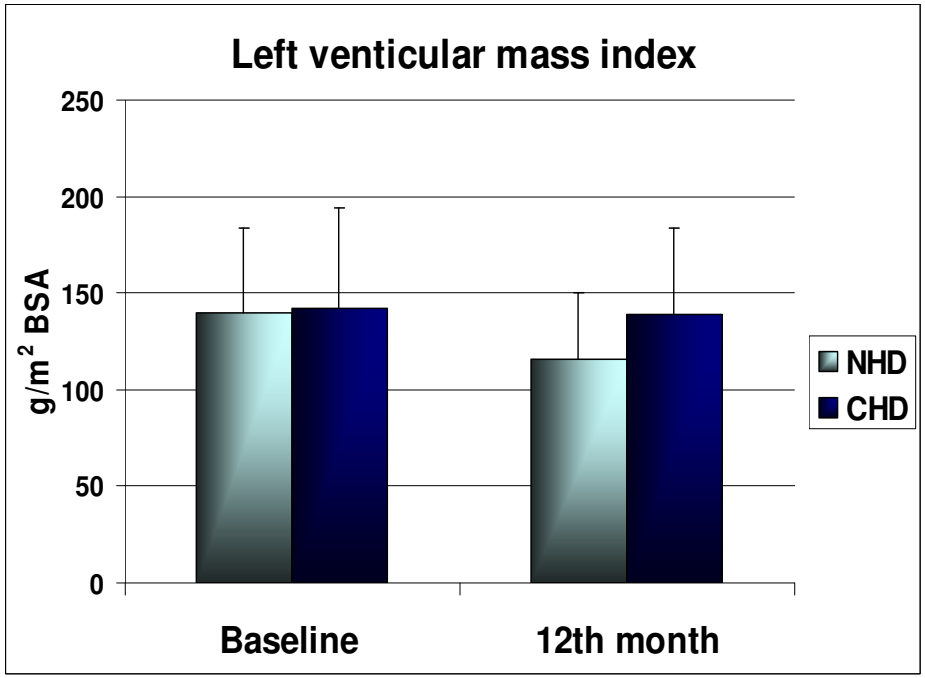


- Serum P levels decreased from 4.59±1.31 to 3.83±1.2 mg/dl at 12th month in NHD patients ($p<0.001$)
- Use of P-binder decreased from 83 to 22%

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

Effect of longer HD on cardiac structure

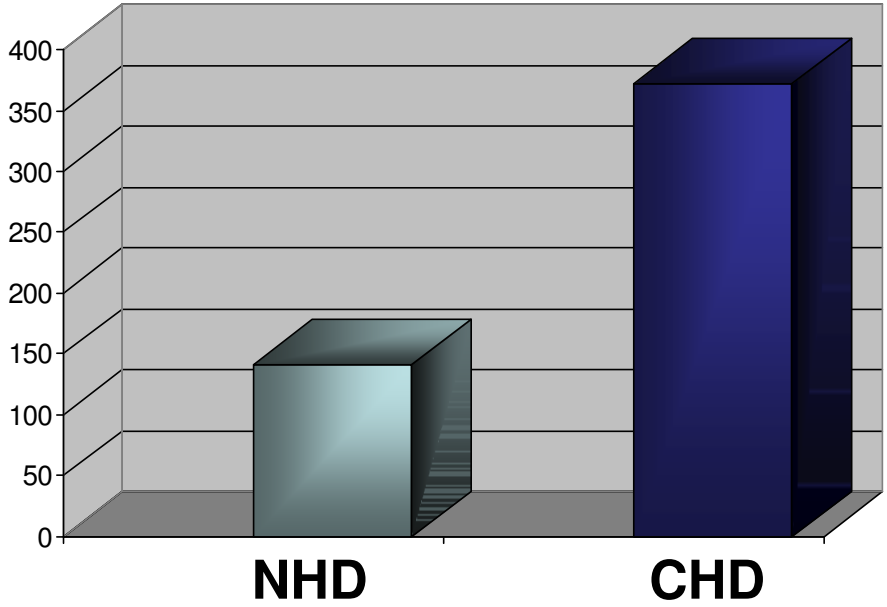




- Decrease in LA diamater in the NHD group (from 2.35 ± 0.40 mm/m^2 BSA to 2.17 ± 0.34, p<0.001)
- Regression in LV mass index in the NHD group (from 140 ± 44 g/m^2 BSA to 116 ± 34, p<0.001)

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

Effect of longer HD on progression of coronary artery calcification



	NHD	CHD	p
Delta median CACs (interquartile range)	141 (67-291)	372 (142-695)	<0.01

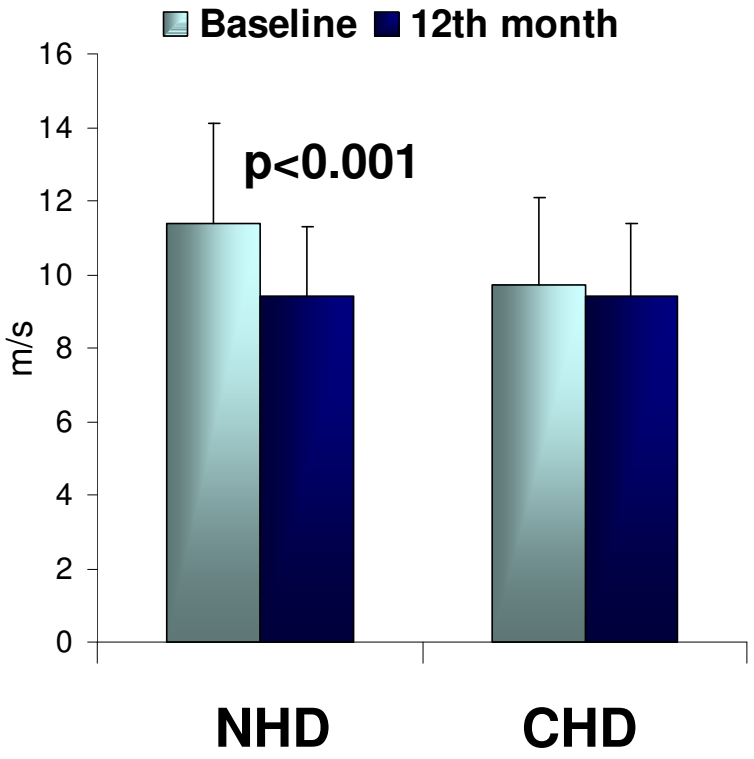
- Lower progression rate with NHD in patients with moderate to severe vascular calcification

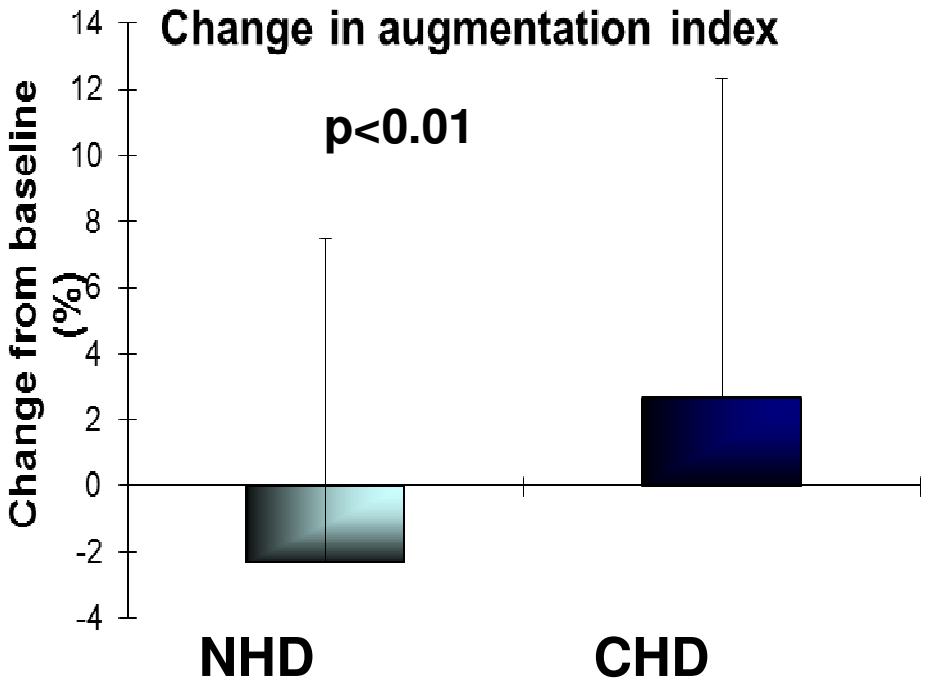
- Serum phosphate was predictor for CAC progression

(Exp-B 2.05, 95% CI 1.46-2.90, p <0.001)

Duman S et al, ASN Congress 2008

Effect of longer HD on arterial stiffness

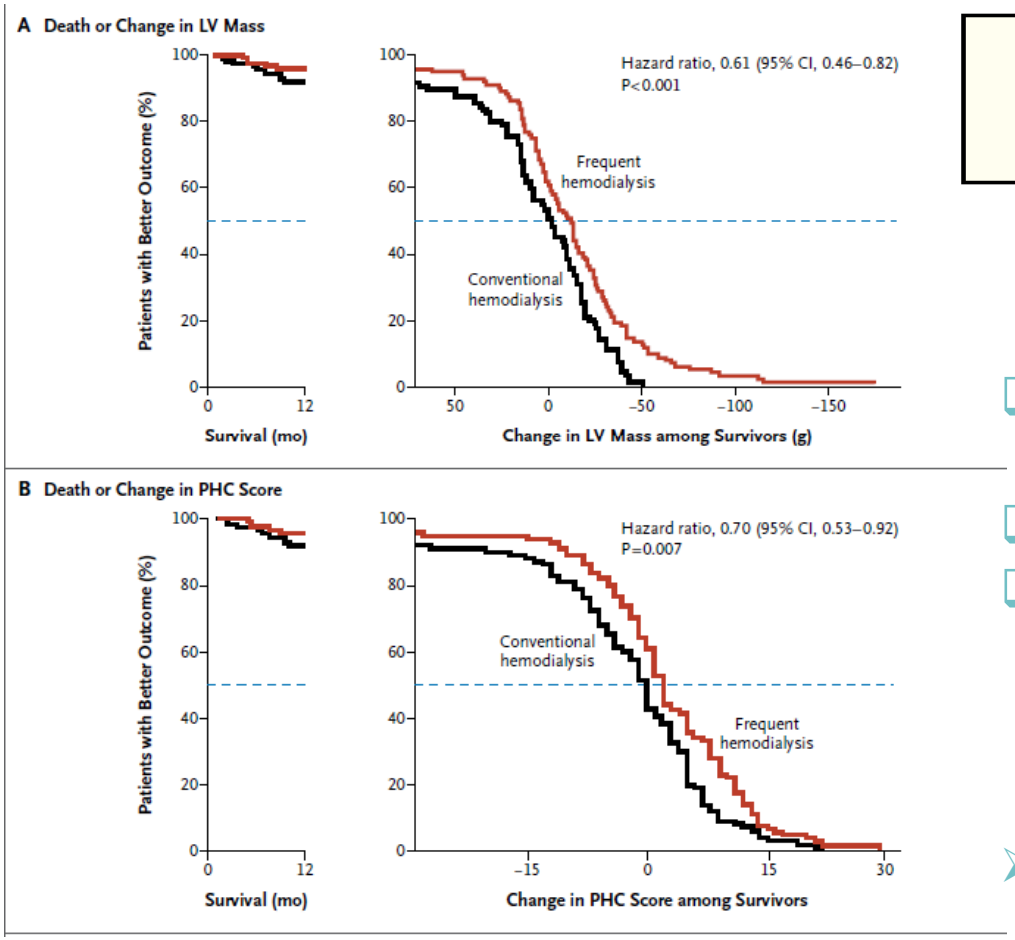




- Decrease in PWV with NHD
- Decrease of AIx in NHD and increase in CHD
- Serum P predictive for changes *(ß-coefficient 0.349, t 2.58, p <0.01)*

Sezis M et al, Atherosclerosis, in press

More frequent hemodialysis



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 9, 2010 VOL. 363 NO. 24

In-Center Hemodialysis Six Times per Week versus Three Times per Week

The FHN Trial Group*

- RCT, in-center HD six times versus three times per week
- 245 pts, 12 mo follow-up
- Primary outcomes:
  - Death or change in LVM
  - Death or change in physical-health composite score

➢ 12.7±2.2 versus 10.4±1.6 hours/week

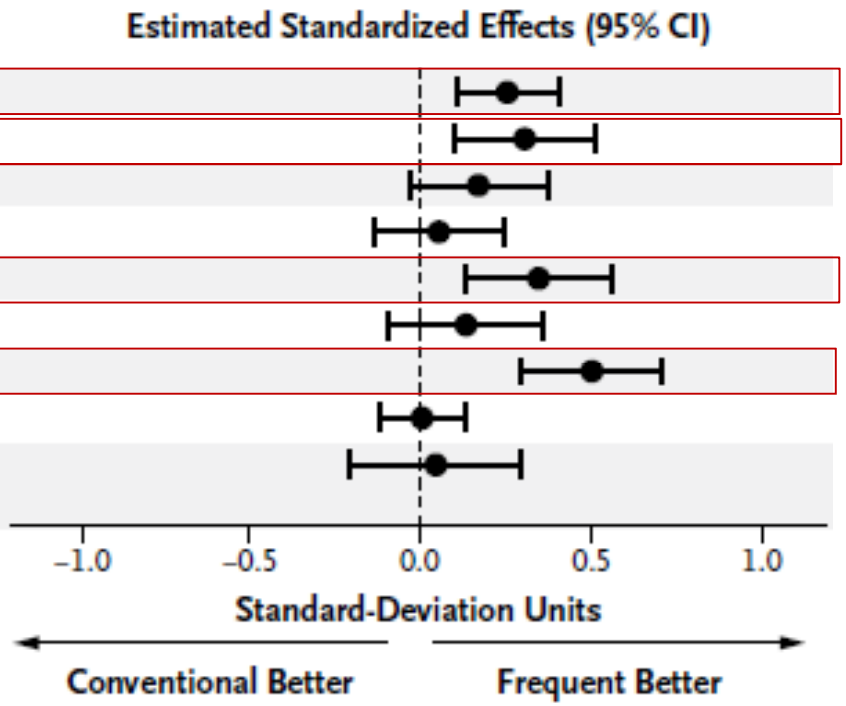
- Frequent HD is associated with favorable primary outcomes

(HR 0.61, 95% CI 0.46-0.82 p<0.001)(HR 0.70, 95% CI 0.53-0.92, p=0.007)

FHN Trial Group, N Engl J Med 2010; 363: 2287

C Main Secondary Outcomes

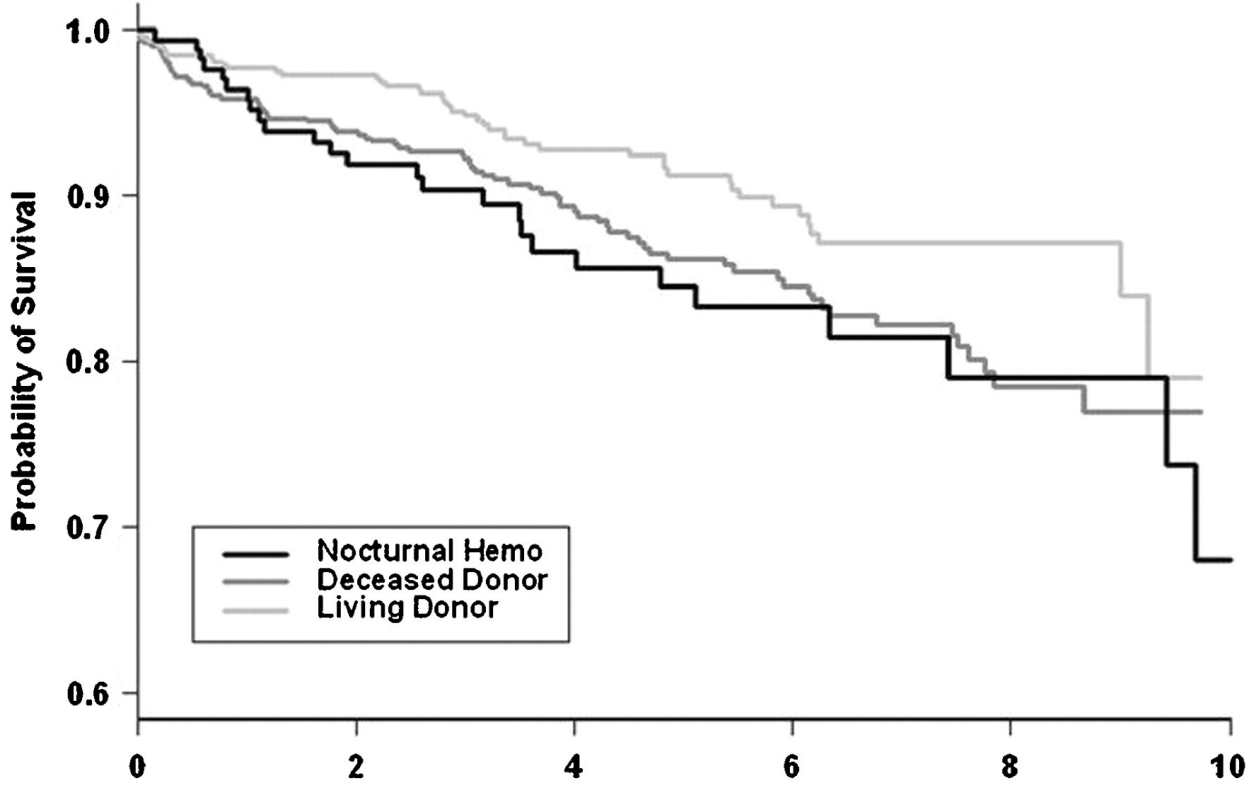
Outcome	Effect Measure
LV mass	Mean decrease
Physical-health composite score	Mean increase
Beck Depression Inventory score	Mean decrease
Predialysis albumin	Mean increase
Predialysis phosphorus	Mean decrease
ESA dose	Mean decrease in log
Predialysis systolic blood pressure	Mean decrease
Trail Making Test Part B	Negative log relative risk
Death or hospitalization unrelated to vascular access	Negative log hazard ratio



- Better blood pressure control
- Decrease in LV mass
- Improvement of physical-health composite score
- Decrease in predialysis phosphorus level
- *More vascular access interventions (HR 1.71; 95%CI 1.08-2.73)*

FHN Trial Group, N Engl J Med 2010; 363: 2287

Frequent nocturnal HHD versus cadaveric and living-related transplantation



- With nocturnal HHD, a survival rate similar to cadaveric kidney transplantation

Pauly RP, Nephrol Dial Transplant 2009; 24: 2915

HIGH FLUX DIALYSER &

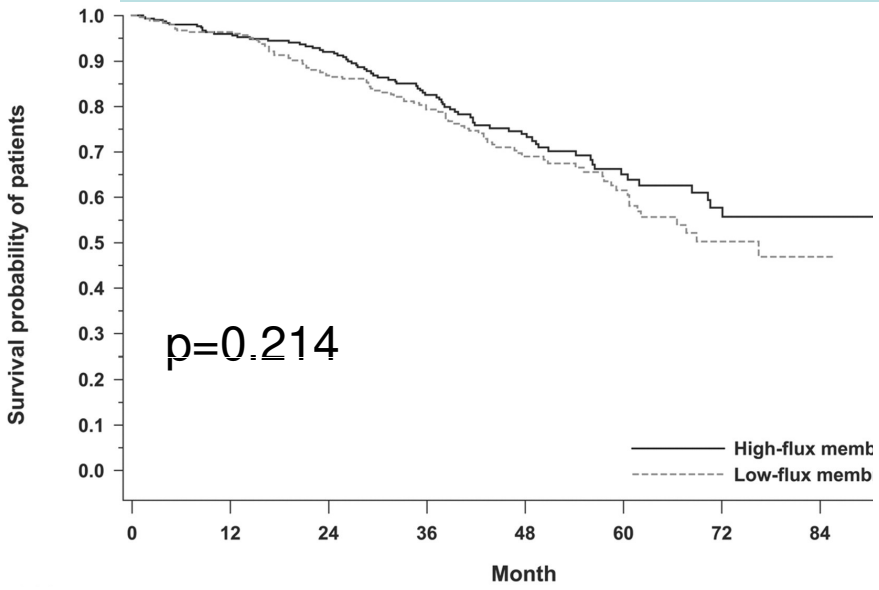
ULTRA-PURE DIALYSATE

High flux membranes and ultra-pure dialysate

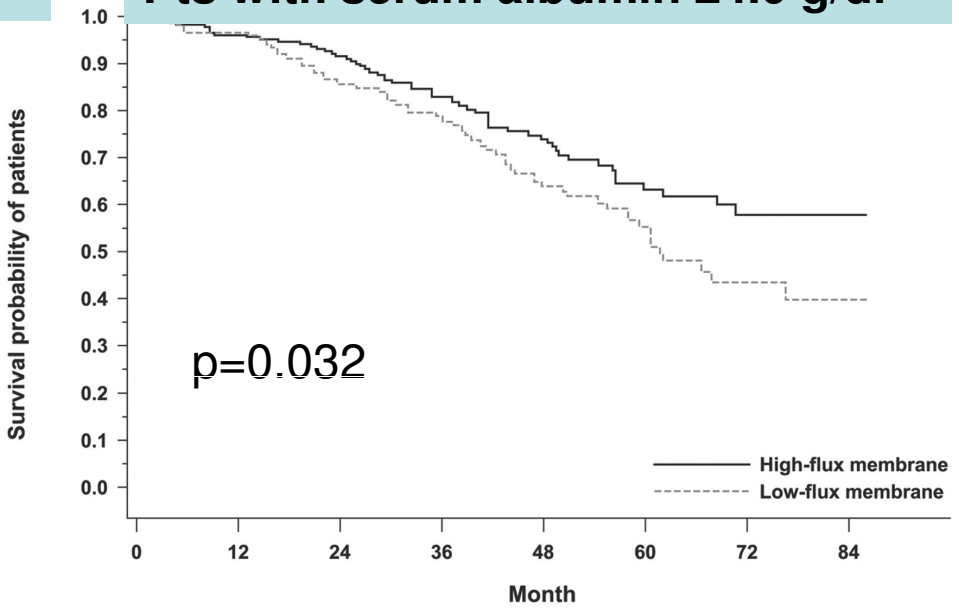
- Both high-flux (HF) membranes and ultra-pure dialysate (UD) have been shown to improve some outcomes
- With respect to survival, UD has never been investigated
- HF membranes have been found superior regarding survival in some subgroups:
  - HEMO: Patients with more than 3 years of HD
  - MPO: Patients with hypoalbuminemia (≤ 4g/dl) and patients with diabetes

Membrane Permeability Outcome Study

All patients



Pts with serum albumin ≤4.0 g/dl



- Randomization of 738 patients stratified by albumin ≤4 and >4 g/dl to HF and LF, mean follow-up 3.0±1.9 years
- No significant difference between HF and LF in overall group
- Higher survival rate in HF group among patients with serum albumin ≤4.0 g/dl
- Better survival with HF in diabetics

Locatelli F, J Am Soc Nephrol 2009; 20: 645

EGE STUDY

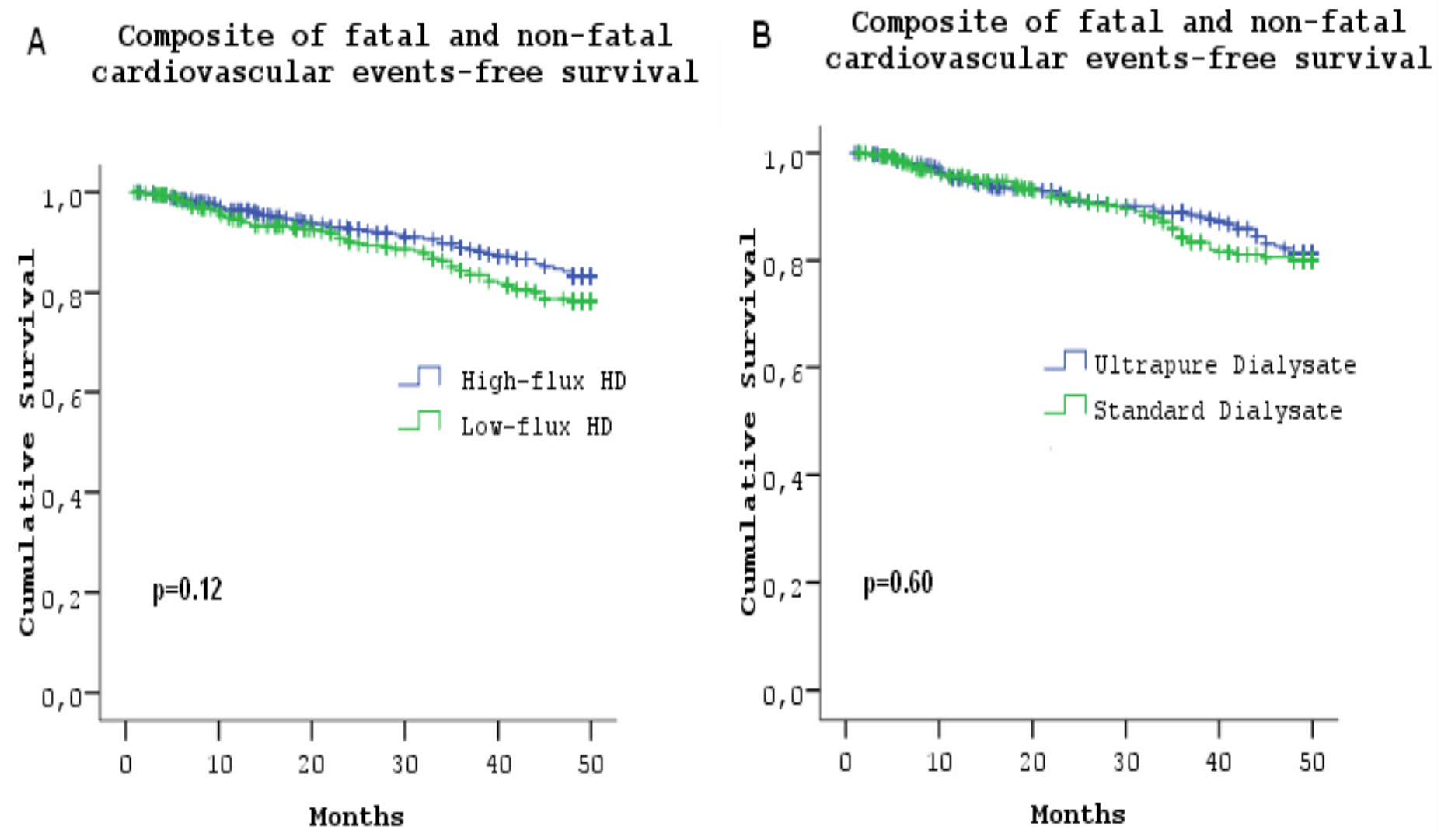
- Prospective, randomized, controlled study to compare high flux versus low flux membrane use and ultra-pure versus standard dialysate use **together**, **in a population treated with strict volume control policy**

ClinicalTrials ID, CT00295191

- 704 prevalent HD patients, 3 years follow-up
- Randomization to HF or LF, then UD or SD, 2x2 factorial design
- No difference between groups regarding baseline parameters
- Primary end-point composite of fatal and non-fatal CV events

Asci G, ASN Congress Late Breaking Clinical Trials 2010

Primary Outcome



Overall and CV survival flux and dialysate groups

	HF	LF	p
▪ Overall survival (%)	78.7	72.4	0.09
▪ CV survival (%)	88.9	84.9	0.14

❑ A trend for better CV event-free, CV and overall survival in HF vs LF

	UD	SD	p
▪ **CV survival** (%)	86.6	87.2	0.94
▪ **Overall survival** (%)	75.3	75.9	0.82

❑ No difference between UD and SD groups regarding CV event-free, CV and overall survival

Time-averaged laboratory values in the flux and the dialysate groups

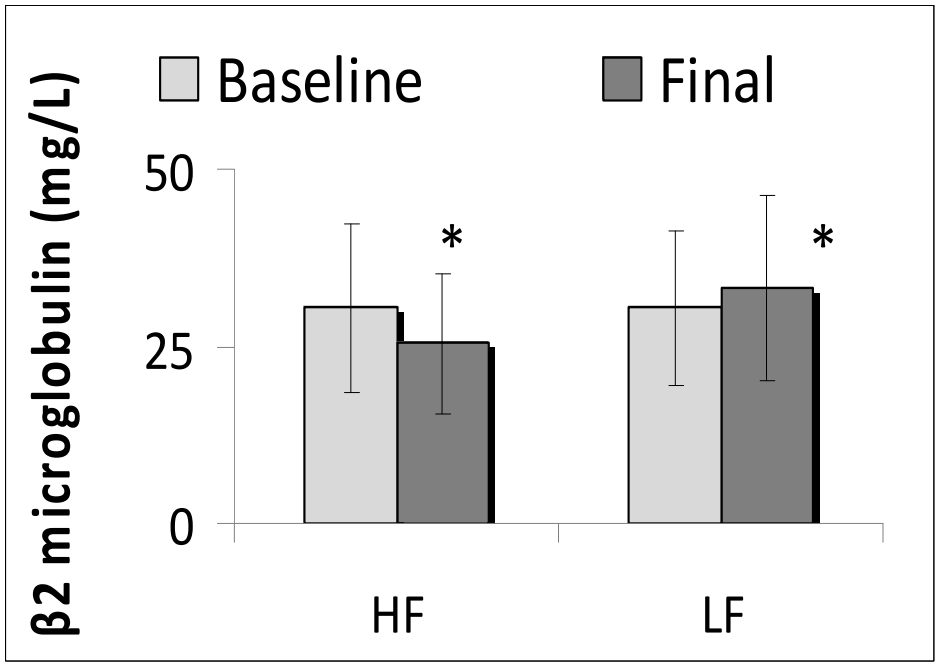
	HF (n=352)	**LF** (n=352)	**p**
Triglyceride (mg/dl)	**165 ± 85**	**185 ± 119**	**0.01**
Hemoglobin (g/dl)	**11.2 ± 1.0**	**11.0 ± 1.0**	**0.02**
Ferritin (ng/ml)	**600 ± 299**	**652 ± 340**	**0.03**

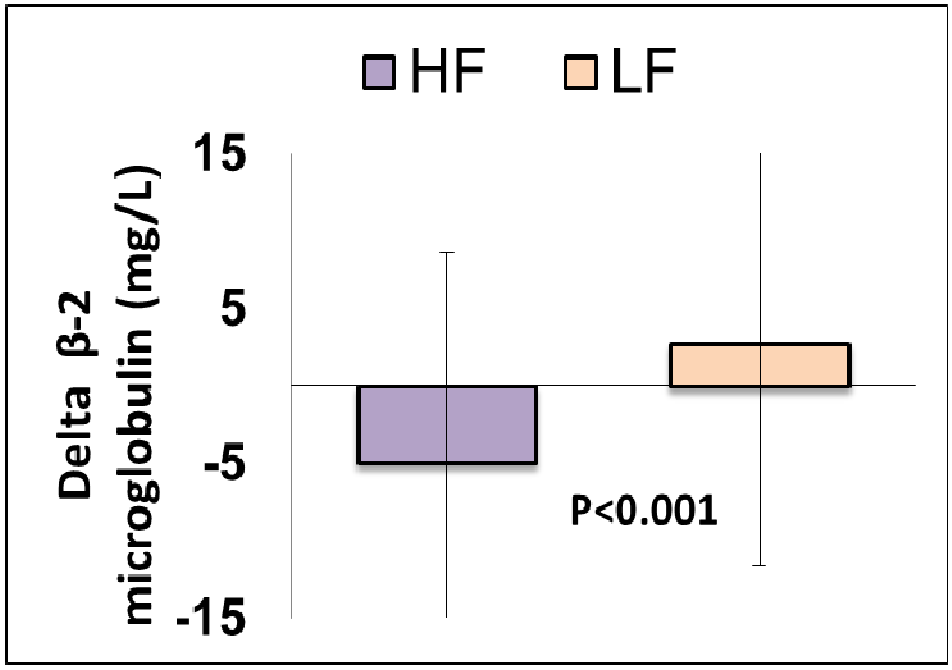
❑ Better anemia management and lipid profile with HF

	UD (n=352)	**SD** (n=352)	**p**
Erythropoietin dose (IU/week)	**2213 ± 2006**	**2523 ± 2021**	**0.04**

❑ Reduction in Epo requirement with use of ultra-pure dialysate

β_2 microglobulin in the dialyser groups





*:p<0.001 and 0.007 in the flux groups

- Reduction in β-2 microglobulin level with HF, whereas an increase in the LF

Patients with arterio-venous fistula (n=576)

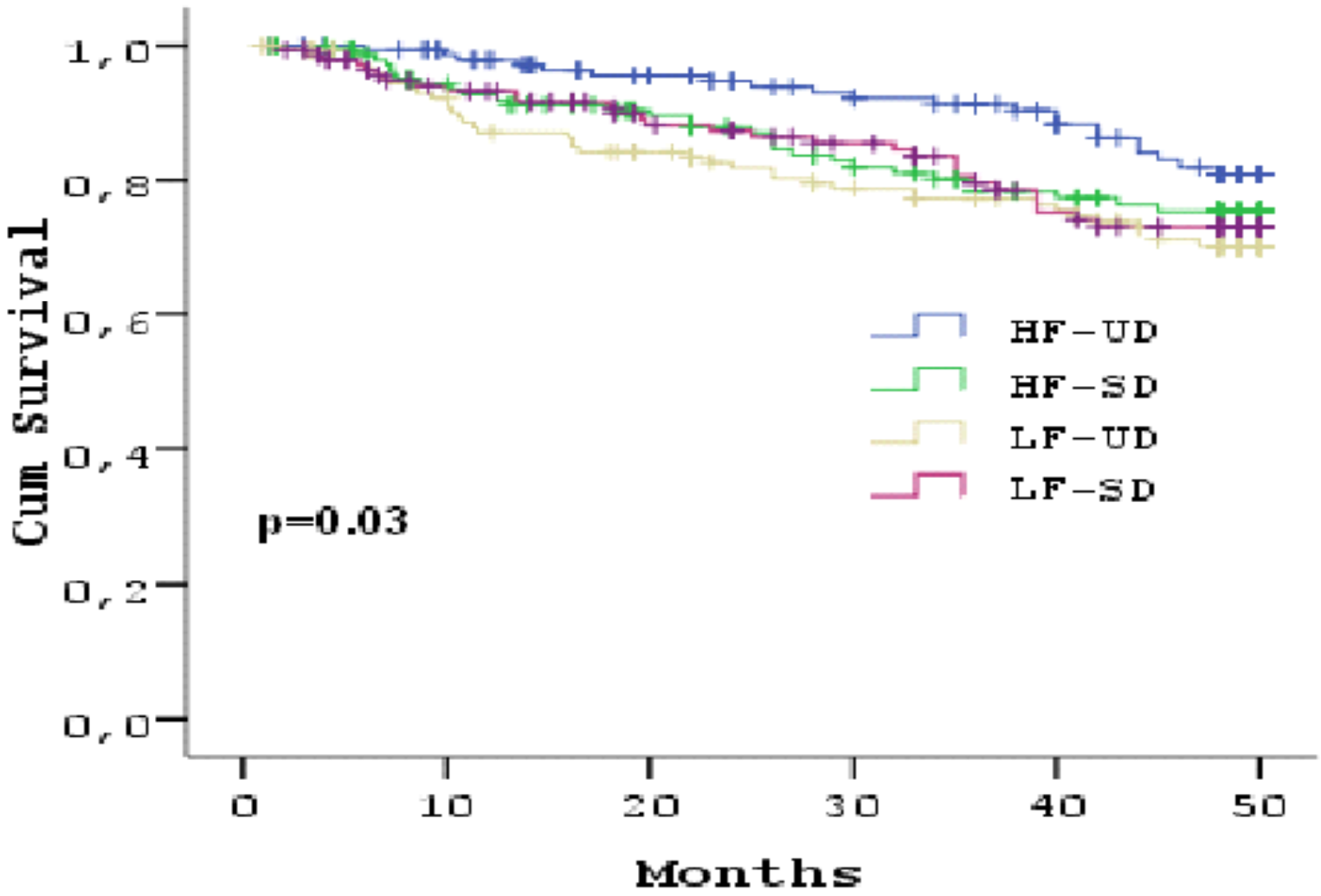
	HF	**LF**	p
Composite CV event-free survival (%)	89.3	82.9	0.02
Overall survival (%)	82.4	75.9	0.04
CV survival (%)	90.7	85.3	0.03

- HF was associated with a 39% decrease in composite CV events (p=0.03).

(In Cox-regression analysis adjusted for age, gender, diabetes, CVD history and time on dialysis)

- Better CV event-free, CV and overall survival by high flux use in patients with AV fistula

Combined treatment with HF and UD had best overall survival rate in patients with AV fistula



HEMODIAFILTRATION

Benefits by hemodiafiltration

- ✓ Enhanced small, middle and larger solute clearance
- ✓ Better intradialytic hemodynamic stability
- ✓ Reduced inflammatory markers
- ✓ Improved phosphate control
- ✓ Increased erythropoietin responsiveness
- ✓ Better beta-2 microglobulin removal and lower risk for carpal tunnel syndrome

Survival with on-line HDF

- Several observational studies have suggested survival benefit with ol-HDF

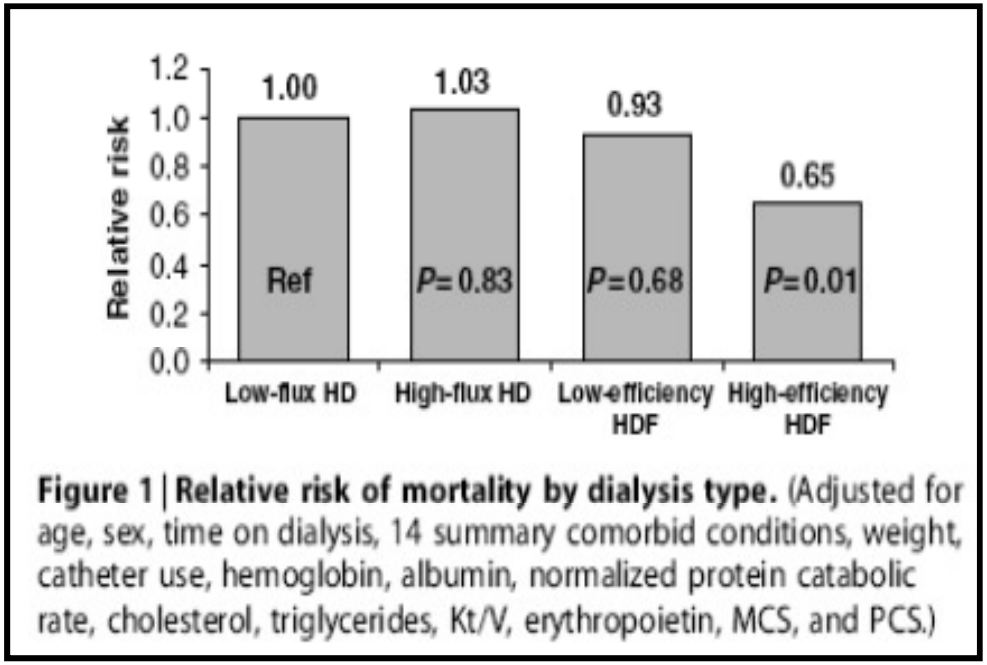
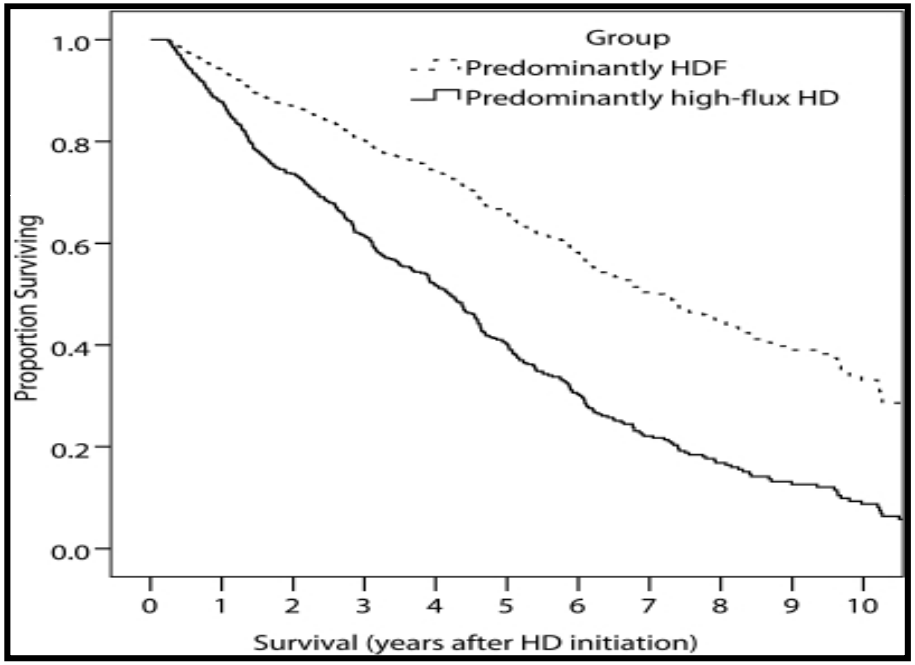


Figure 1 | Relative risk of mortality by dialysis type. (Adjusted for age, sex, time on dialysis, 14 summary comorbid conditions, weight, catheter use, hemoglobin, albumin, normalized protein catabolic rate, cholesterol, triglycerides, Kt/V, erythropoietin, MCS, and PCS.)

Canaud et al. Kidney Int 2006;69:2087-93



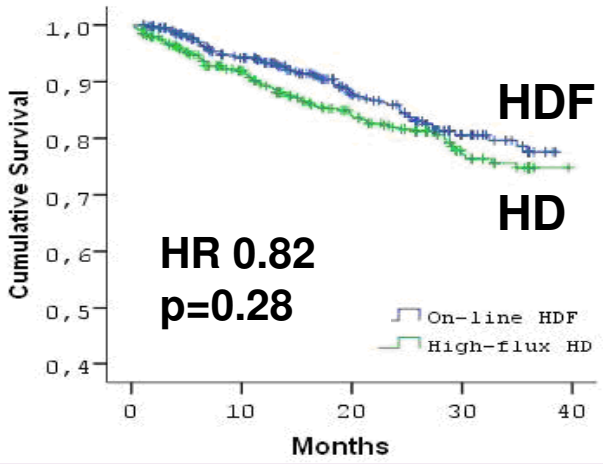
Vilar et al. Clin JASN 2009;4:1944-53

HDF STUDY
PROSPECTIVE RANDOMIZED CONTROLLED STUDY
(Clinicaltrials ID: NCT00411177)

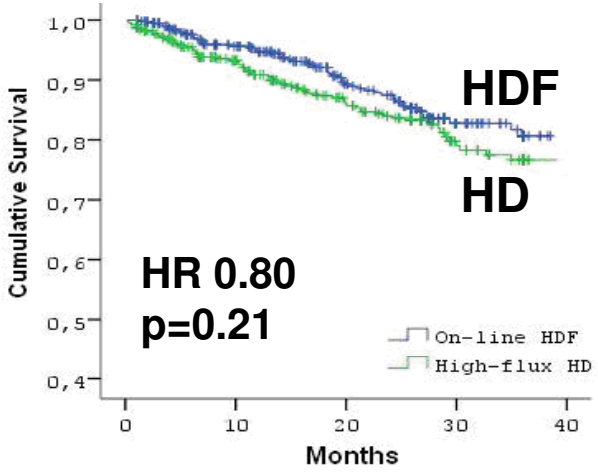
- Randomization of 782 prevalent HD patients to post-dilution ol-HDF or to high-flux HD
- No difference between groups regarding baseline parameters
- Follow-up 2 years
- In the ol-HDF, target substitution volume over 15 L per session
- Primary outcome composite of all-cause mortality and new non-fatal cardiovascular events
- Secondary outcomes CV and overall mortality, intradialytic complications, changes in clinical-laboratory parameters and

Ok E et al, 2011 ERA-EDTA Congress Late Breaking Clinical Trials

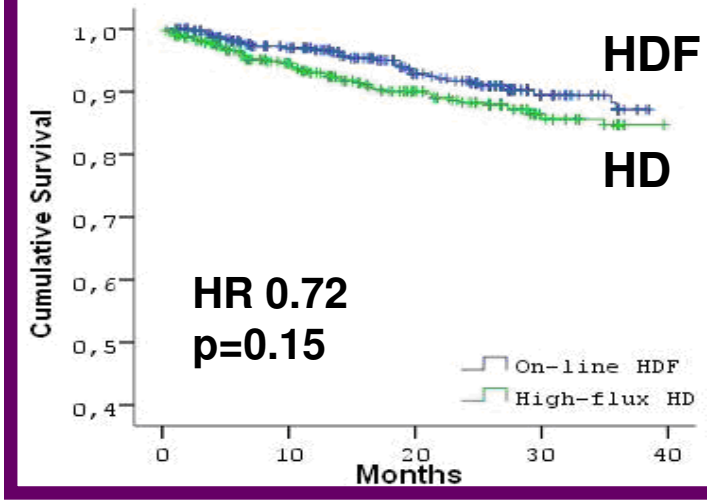
Composite event-free survival



Overall survival



Cardiovascular survival



- No significant difference between HDF and HD regarding
  - composite event-free survival
  - overall survival
  - cardiovascular survival

Follow-up Data

	On-line HDF (n=391)	**High-flux HD** (n=391)	p value
Substitution volume (L/session)	**17.2 ± 1.2**	-	-
Blood flow rate (ml/min)	318 ± 27	303 ± 32	<0.001
Systolic blood pressure (mmHg)	129 ± 13	126 ± 13	<0.001
Interdialytic weight gain (% BW)	3.5 ± 1.9	3.2 ± 1.5	0.01

OL-HDF→ HIGHER BLOOD FLOW, SYSTOLIC BP AND IDWG

Urea (mg/dl)	124 ± 21	129 ± 23	0.002
URR (%)	75.2 ± 4.7	73.2 ± 5.3	<0.001
eKt/V	1.44 ± 0.19	1.33 ± 0.19	<0.001

OL-HDF→ HIGHER SMALL SOLUTE CLEARANCE

Follow-up Data

	On-line HDF (n=391)	**High-flux HD** (n=391)	p value
Albumin (g/dl)	3.93 ± 0.24	3.99 ± 0.27	0.001
Triglyceride (mg/dl)	173 ± 97	191 ± 107	0.01
HDL (mg/dl)	37 ± 11	34 ± 9	0.007

OL-HDF→ LOWER ALBUMIN AND TRIGLYCERIDES, HIGHER HDL-CHOLESTEROL BETTER

ESA dose (U/week)	2282 ± 2121	2852 ± 2706	0.001
Bicarbonate (mEq/L)	22.5 ± 1.8	21.9 ± 2.0	<0.001

OL-HDF→ HIGHER BICARBONATE, LOWER EPO REQUIREMENT

SUBGROUP ANALYSES

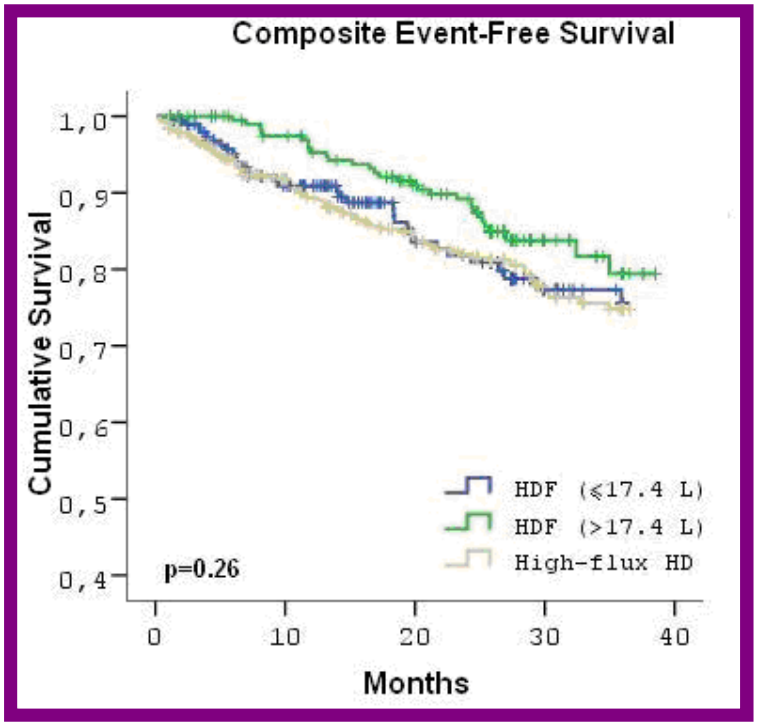
- ol-HDF patients were divided into two groups according to amount of substitution volume (median 17.4 L per session)

HIGH EFFICIENCY OL-HDF ›17.4 L

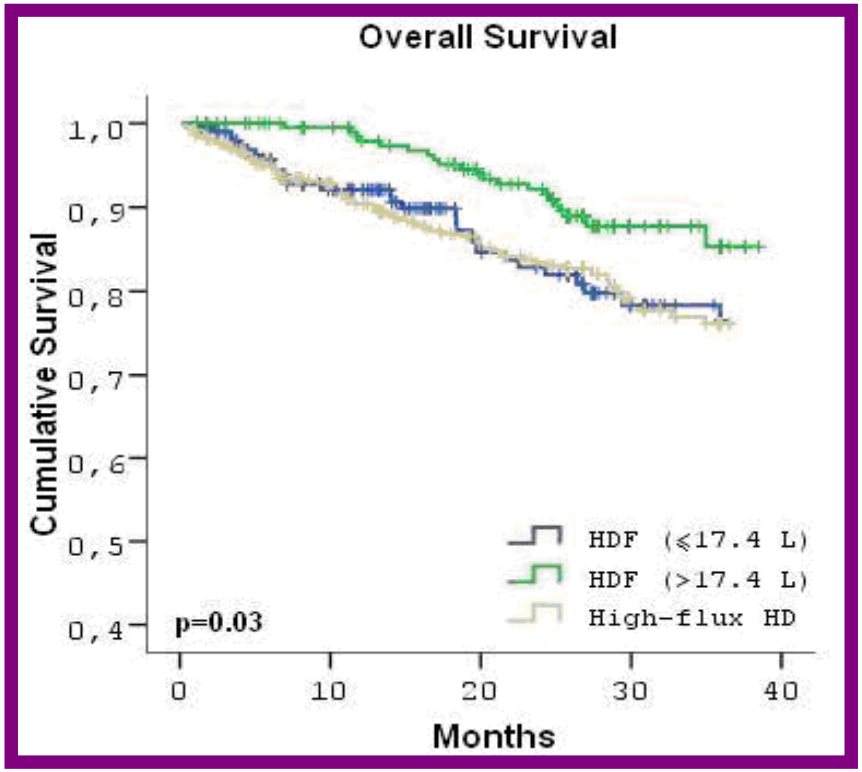
LOW EFFICIENCY OL-HDF ≤17.4 L

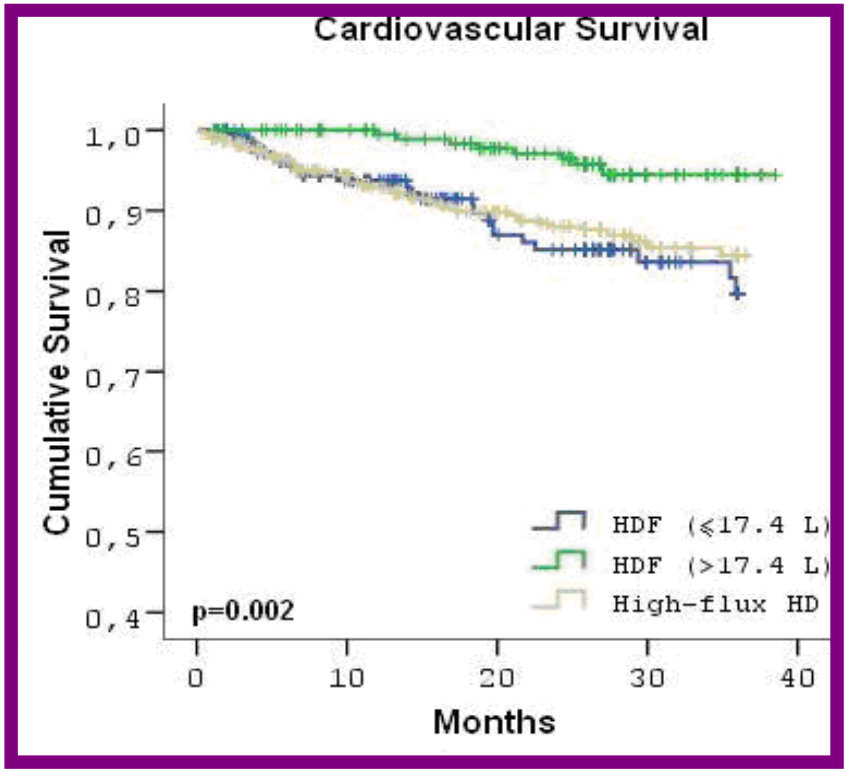
PRIMARY OUTCOME

- No difference in primary outcome between three groups



HIGH EFFICIENCY vs LOW EFFICIENCY oI-HDF
Overall and cardiovascular survival





HIGH EFFICIENCY OL-HDF → BETTER OVERALL AND CARDIOVASCULAR SURVIVAL

HIGH EFFICIENCY VS LOW EFFICIENCY ol-HDF

Baseline characteristics

	HD N=391	LE ol-HDF RF ≤ 17.4 L N=196	HE ol-HDF RF >17.4 L N=195	p
Substitution Volume	-	**16.2 ± 1.0**	**18.1 ± 0.68**	
Diabetes (%)	33	42	32	0.02
Blood flow rate (ml/min)	294 ± 44	281 ± 38	304 ± 48	0.001

MORE DIABETICS IN THE LOW EFFICIENCY OL-HDF GROUP AND HIGHER BLOOD FLOW RATE IN THE HIGH EFFICIENCY OL-HDF GROUP

Albumin (g/dl)	3.85 ± 0.38	3.75 ± 0.34	3.90 ± 0.33	<0.001
Hemoglobin (g/dl)	11.4 ± 1.44	11.7 ± 1.6	11.2 ± 1.41	0.002
Phosphate (mg/dl)	4.88 ± 1.48	5.13 ± 1.55	4.72 ± 1.29	0.01

LOWER ALBUMIN, HIGHER HEMOGLOBIN AND PHOSPHATE IN THE LOW EFFICIENCY OL-HDF

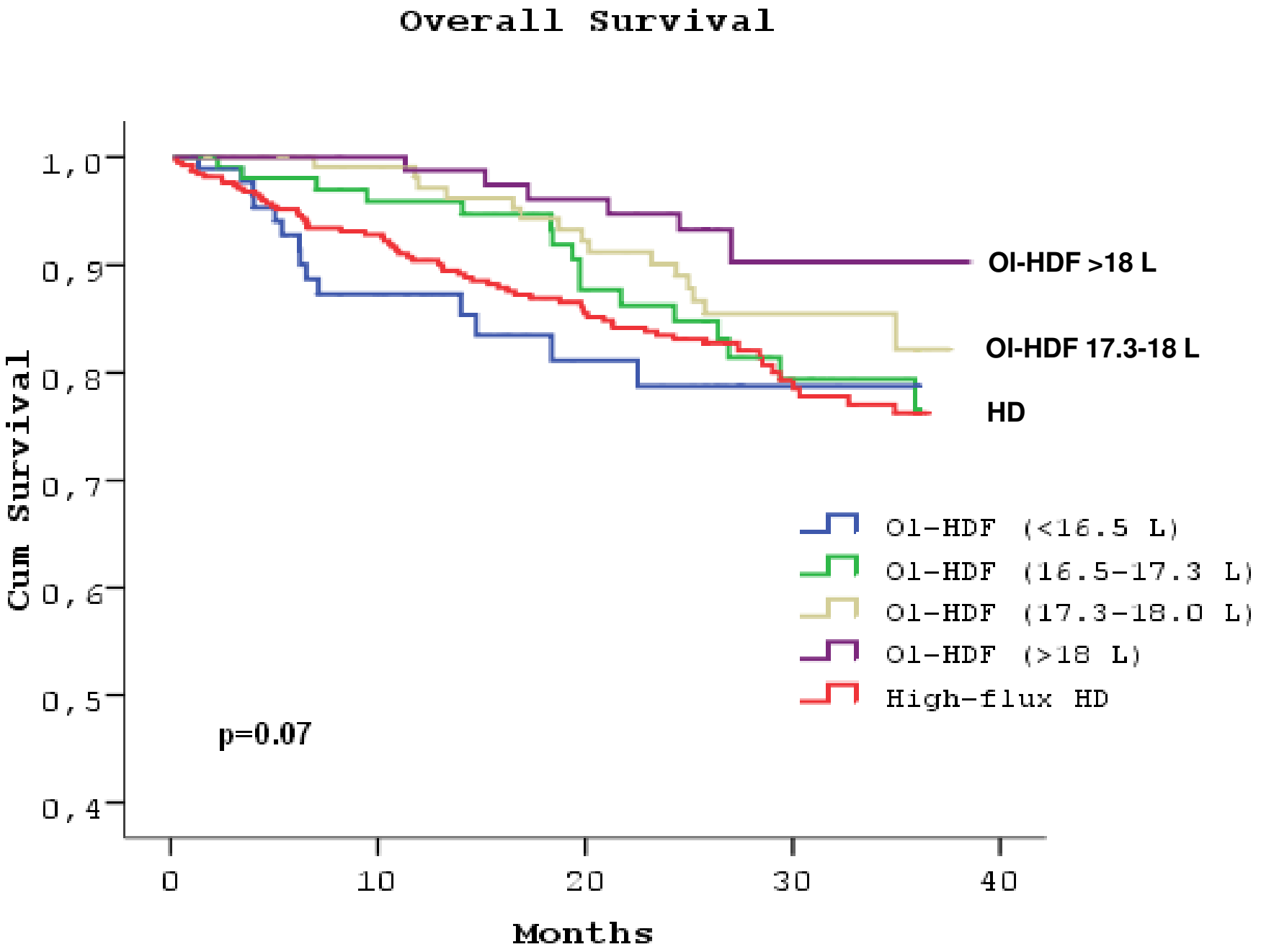
HE ol-HDF versus LE ol-HDF and HD
Multivariate analysis for overall mortality

	Unadjusted **HR** (95% CI)	**Model 1** **HR** (95% CI)	**Model 2** **HR** (95% CI)
High-flux HD	Reference	Reference	Reference
HDF with RF ≤17.4 L	0.99 (0.64-1.53) p=0.54	1.17 (0.73-1.88) p=0.36	1.10 (0.68-1.76) p=0.69
HDF with RF > 17.4 L	**0.54** (0.33-0.88) p=0.01	**0.57** (0.33-0.96) p=0.04	**0.54** (0.31-0.93) p=0.02
Age (per year)		1.05 (1.03-1.07) p<0.001	1.05 (1.03-1.07) p<0.001
Presence of diabetes		1.73 (1.15-2.60) p=0.007	1.88 (1.25-2.84) p=0.002
Albumin (per g/dl)		-	0.49 (0.28-0.85) p=0.01

Model 1: Adjusted with age, sex, DM, CVD, time on HD, vascular access, blood flow rate, IDWG

Model 2 – fully adjusted: Model 1+ hemoglobin, albumin, phosphate and urea reduction rate

ol-HDF → 46% RR REDUCTION IN OVERALL MORTALITY


Overall Survival
Cum Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0
10
20
30
40
Months
p=0.07
Ol-HDF >18 L
Ol-HDF 17.3-18 L
HD
Ol-HDF (<16.5 L)
Ol-HDF (16.5-17.3 L)
Ol-HDF (17.3-18.0 L)
Ol-HDF (>18 L)
High-flux HD

- No difference between HDF and HD in the whole group
- Subgroup of patients treated with high convection volumes has better survival
- Although survival benefit with high dose HDF persisted in multivariate analyses after fully correction with several confounders (including blood flow), results should be cautiously evaluated because this subgroup analysis was not planned in the study protocol

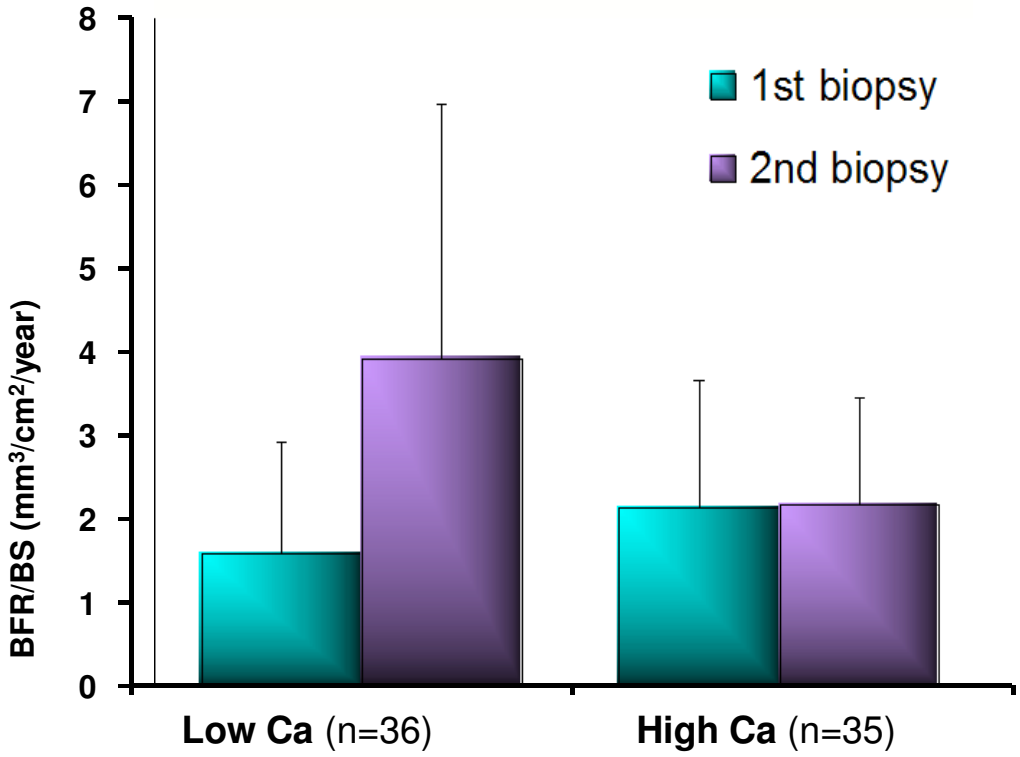
TO MANIPULATE DIALYSATE CONTENT

DIALYSATE CALCIUM STUDY

- Prospective, randomized, controlled study
  ClinicalTrials ID, (ID NCT00297219)
- Intervention: Lowering dialysate Ca level from 1.5-1.75 mmol/L to 1.25 mmol/L in patients with PTH levels below 300 pg/ml
- Randomization of 425 HD patients to 1.25 or 1.75 mmol/L dialysate Ca
- Two years follow-up; bone biopsy and multi-slice CT at baseline and 24th month
- End-points: Change in bone histomorphometry and progression of CAC score

Ok E, ASN Congress Late Breaking Clinical Trials 2008

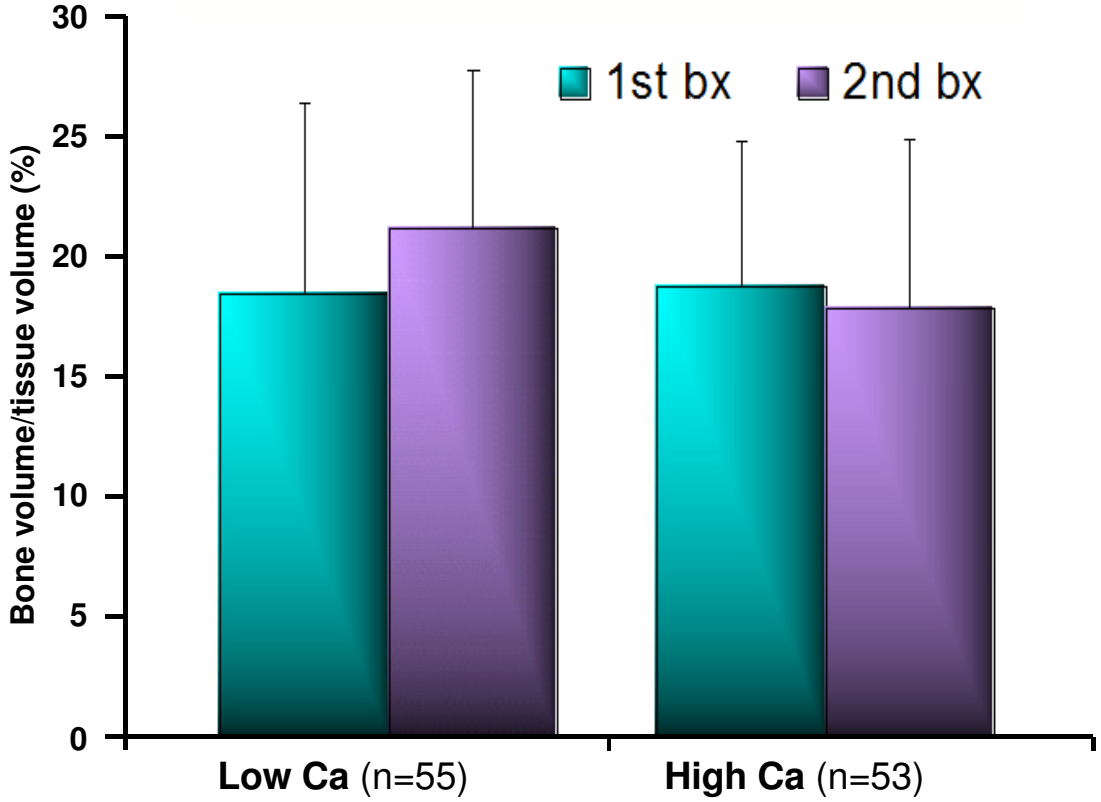
Dramatic increase in bone formation rate in the Low Ca group



1st biopsy	1.58±1.35	↑	2.13±1.54
2nd biopsy	3.93±3.05		2.16±1.29
	p<0.0001		p=0.92

Ok E. ASN Congress 2008, Late Breaking Clinical Trials Session

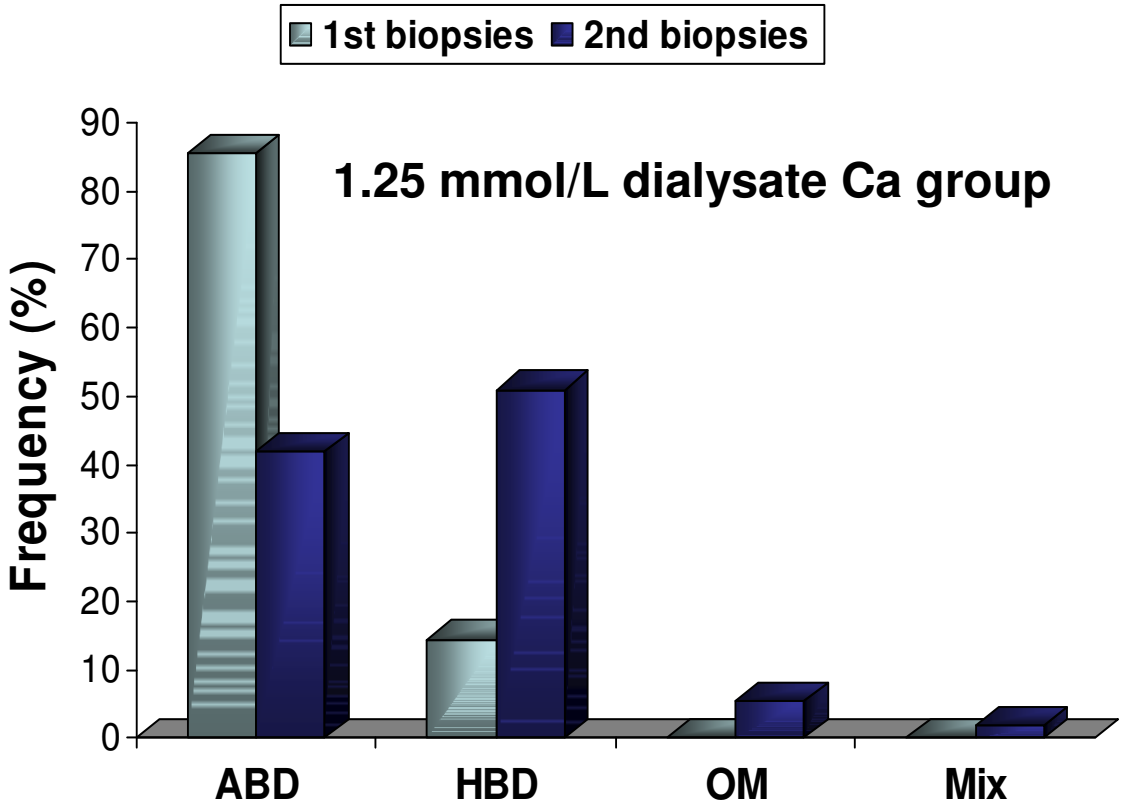
Bone volume increased in the Low Ca group



	Low Ca (n=55)	High Ca (n=53)
1st biopsy	18.6±8.0	18.9±6.1
2nd biopsy	21.3±6.6	18.0±7.1
	p=0.02	p=0.43

Ok E. ASN Congress 2008, Late Breaking Clinical Trials Session

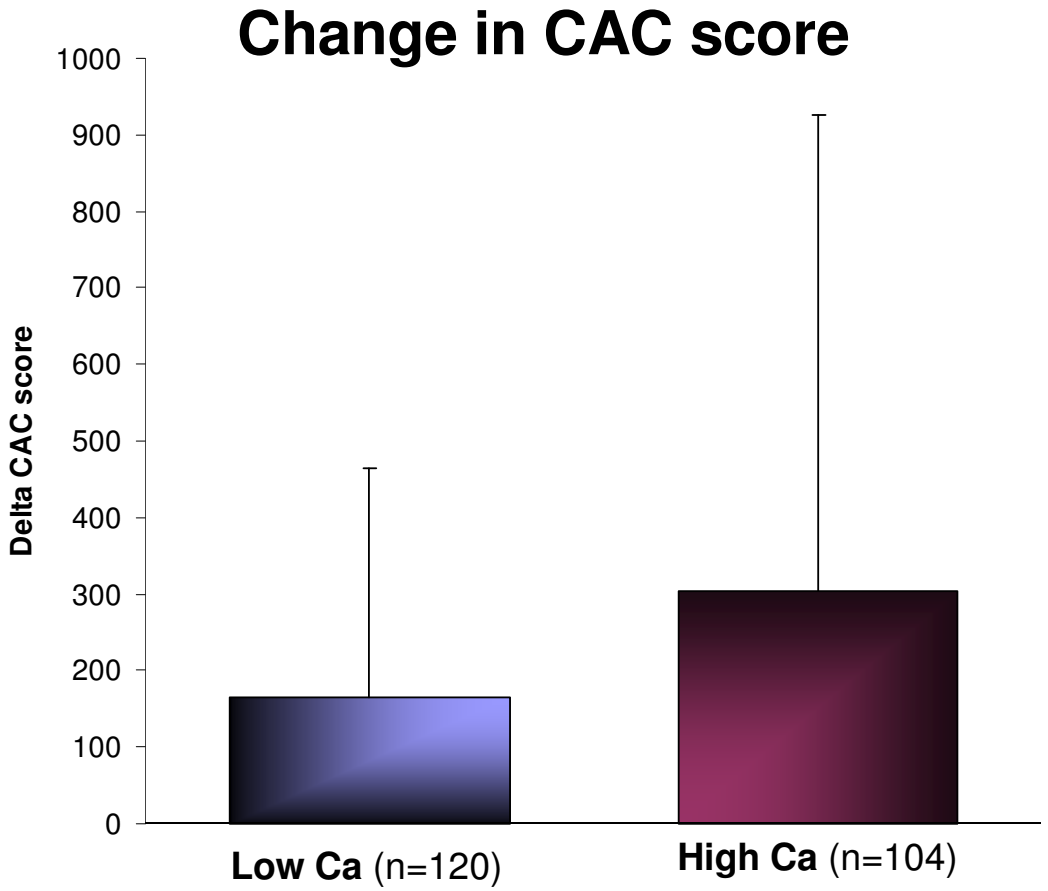
Lowering Ca exposure via dialysate improves adynamic bone disease



- **ABD decreased** from 85% to 42%
- **Mild HBD increased** from 15% to 51%

Ok E. ASN Congress 2008, Late Breaking Clinical Trials Session

Lower progression rate of CAC in the Low Ca group



ΔCACs	164±299	303±624	p=0.03

Ok E. ASN Congress 2008, Late Breaking Clinical Trials Session

CONCLUSION

- Dietary salt restriction and strict volume is associated with successful BP control, decreased intradialytic hypotension and better cardiac geometry and functions

- More dialysis, especially combination of more frequent and longer HD sessions at home or in center improves majority of outcomes, including survival

Conclusion

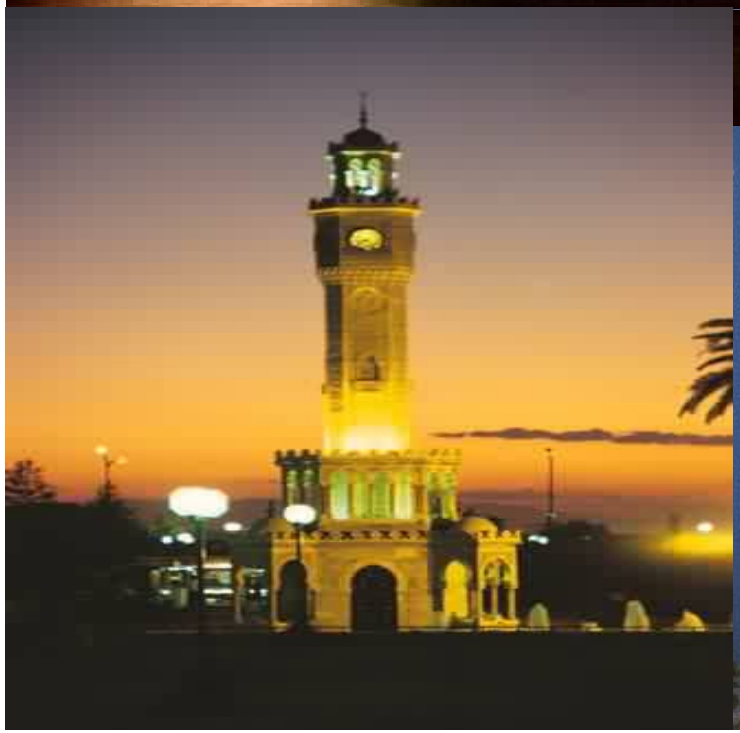
- If there is no possibility to increase duration and/or frequency of HD, combination of high-flux and ultra-pure dialysate seems to provide better survival in patients with AV fistula / longer HD vintage / lower serum albumin / diabetes
- HF membrane use provides better anemia management, lipid profile and β-2 microglobulin clearance
- Ultra-pure dialysate use reduces Epo requirement. It is also associated with lower CRP levels in patients with HD vintage longer than 3 years

Conclusion

- Post-dilution ol-HDF provides higher small solute clearance, better lipid profile, reduction in Epo requirement
- Post-dilution ol-HDF with high convection volumes may be beneficial to ameliorate survival in the presence of good AV fistula allowing higher blood flow
- To manipulate dialysate content is an important treatment method to improve outcomes; it is effective at no cost

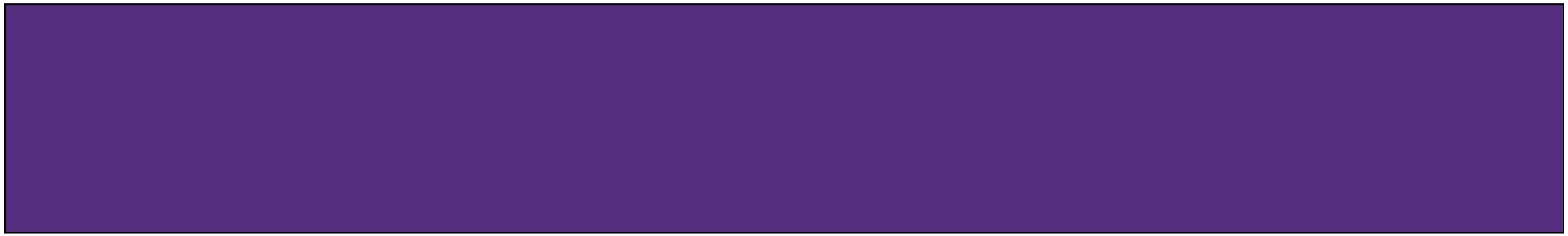
Izmir

Thank you



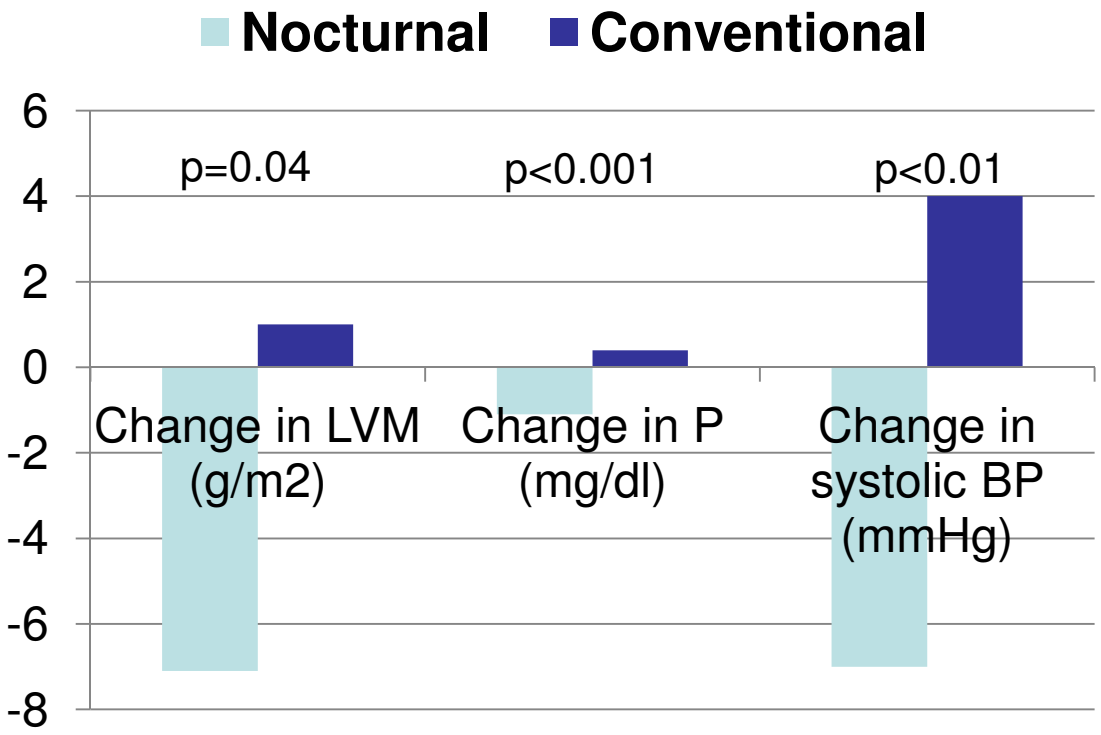
Patients need replacement of kidney functions by «good» dialysis

- Salt restriction, volume control
  - More frequent and/or longer HD session
    - AV fistula & High flux & Ultra-pure
      - *Good* AV fistula & post-dilution ol-HDF with high convection volume (?)



ADDITIONAL SLIDES

Frequent nocturnal HHD *(more frequent and longer)* versus conventional HD



- RCT, six-times nocturnal HHD versus in-center conventional HD
- 52 pts, 12 mo follow-up
- Primary outcome change in LVM

Culleton BF, JAMA 2007; 298: 1291

- Decrease in systolic BP (along with discontinuation of BP medications in 62%) and regression of LV mass
- Reduction of serum P level (with decrease in PO4-binder use in 73%)
- Improvement in kidney-specific domains of quality of life

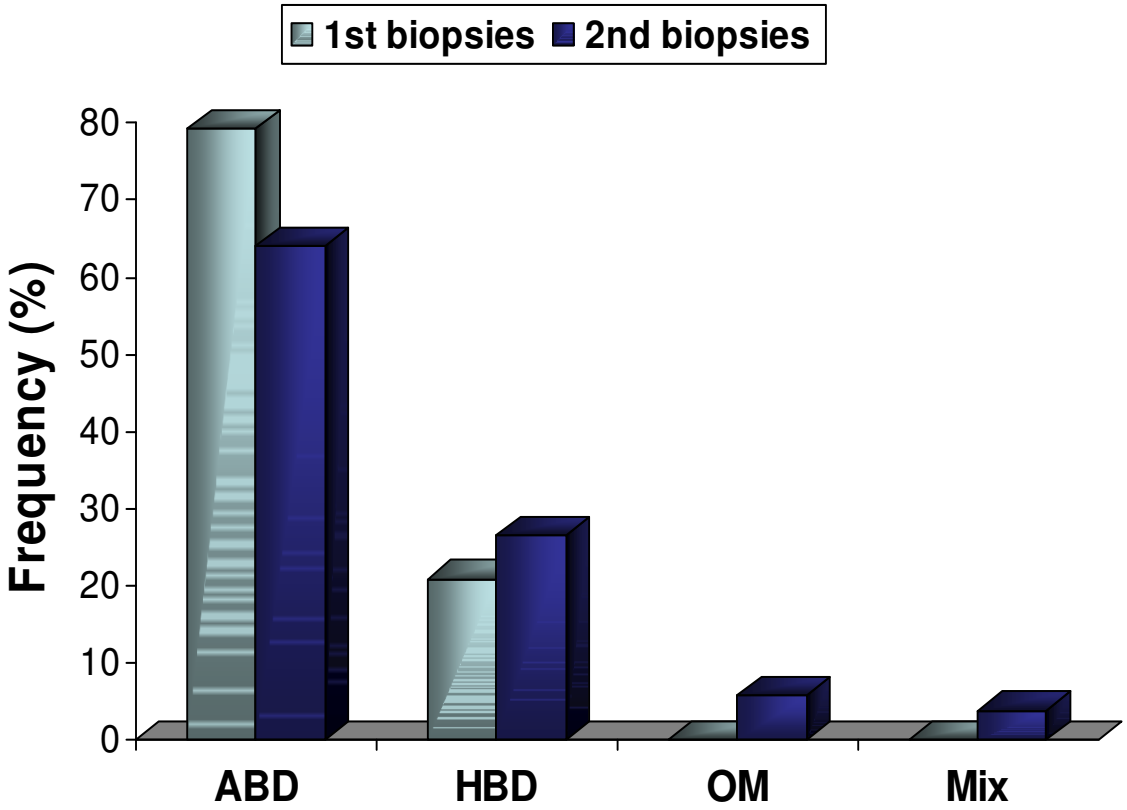
Regression of left ventricular hypertrophy with volume control

- Two echocardiographies in 15 prevalent HD patients with a mean interval of 37±11 months after implementation of volume control policy

	First	Second
• Systolic BP (mmHg)	136 ± 11	101 ± 14
• Diastolic BP (mmHg)	119 ± 8	82 ± 12
• CTi	0.48 ± 0.03	0.43 ± 0.04
• Left atrial diameter (mm/m^2)	22.5 ± 3.1	19.9 ± 4.4
• **LV mass index (g/m^2)**	**175 ± 60**	**105 ± 11**

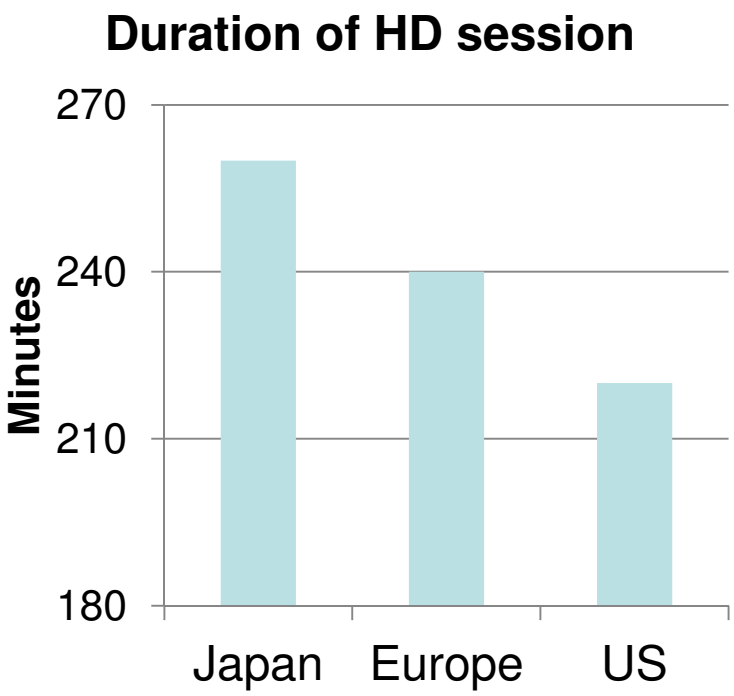
Ozkahya M, Nephrol Dial Transplant 1998

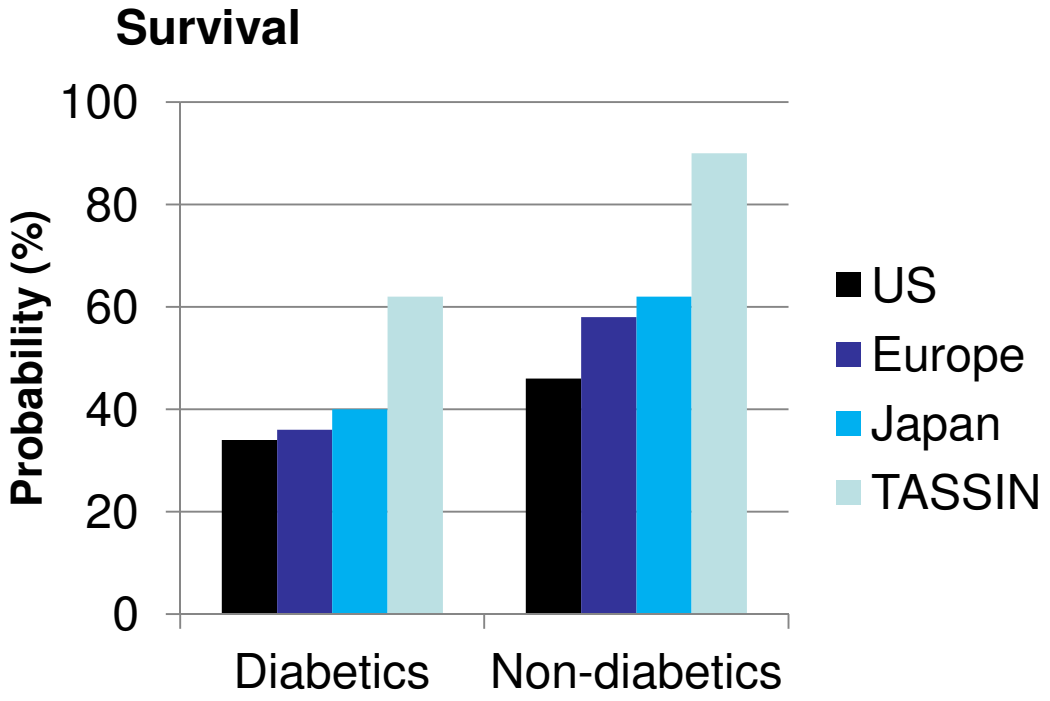
No significant change in High Ca group



Ok E. ASN Congress 2008, Late Breaking Clinical Trials Session

Duration of HD sessions

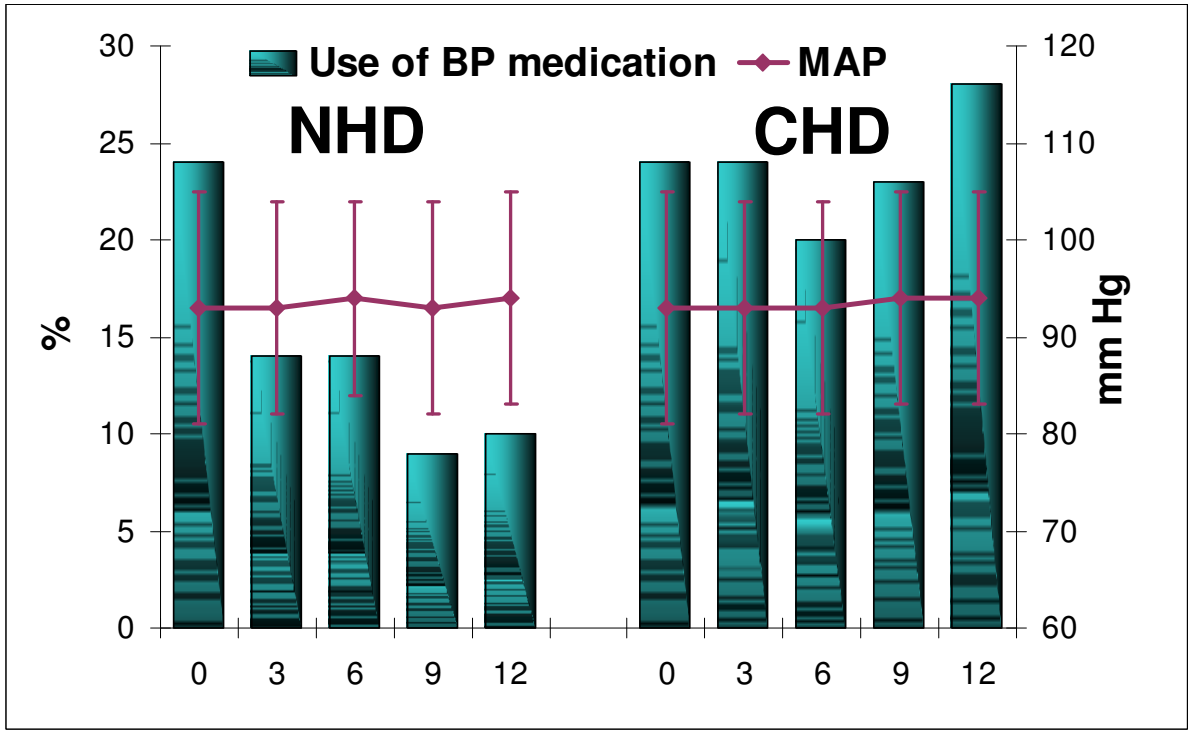




- Regional differences in duration of HD sessions and in survival
- Best survival data with three times 8-h dialysis from Tassin

Hull AR, Am J Kidney Dis 1990; 15:375, Charra B, Kidney Int 1992; 41:1286.

Effect of longer HD on blood pressure control



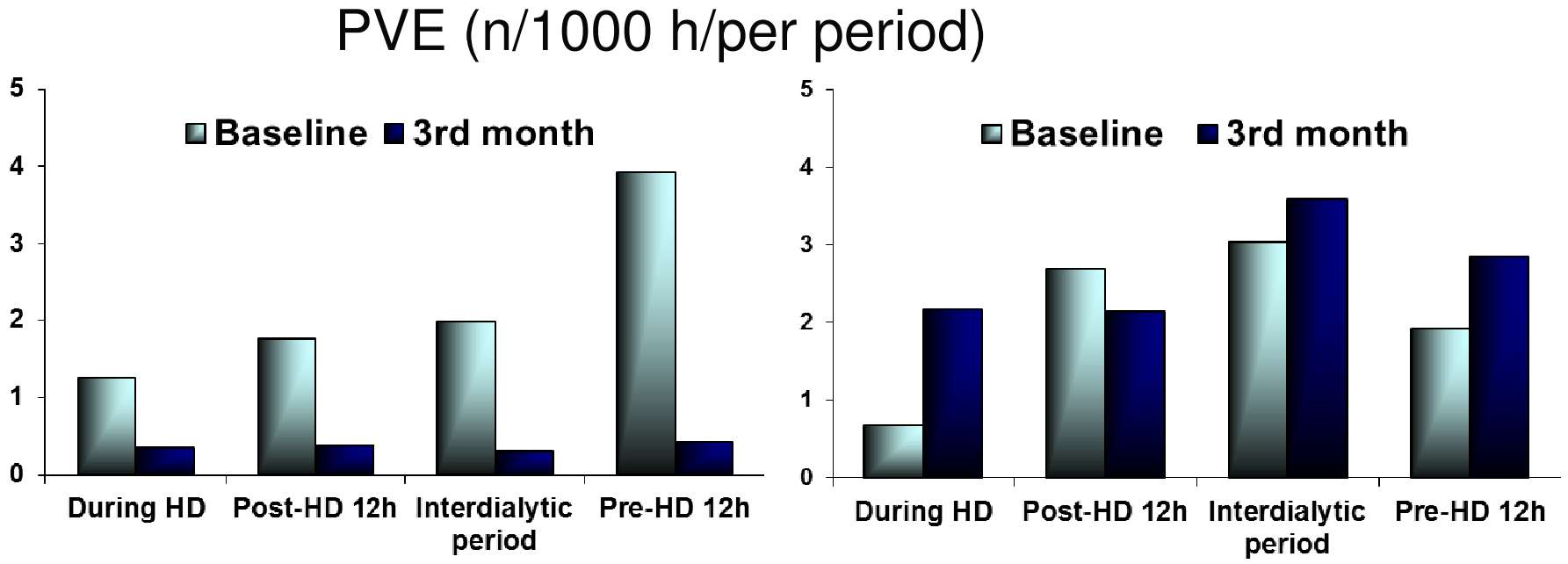
- No change in mean arterial BP in both arms
- Requirement of anti-hypertensive medication decreased from 24% to 8% in the NHD group

Ok E et al, Nephrol Dial Transplant 2011; 26: 1287

	NHD (n=247)	CHD (n=247)
▪ **Mean age** (years)	45.2 ± 13.9	45.8 ± 12.9
▪ **Female**	31.9%	
▪ **Diabetes**	21%	
▪ **HD vintage** (months)	60.6 ± 44.9	59.5 ± 44.4
▪ **Duration of HD session** (min)	455 ± 20 *	236 ± 7
▪ **Blood flow** (ml/min)	240 ± 35 *	292 ± 32

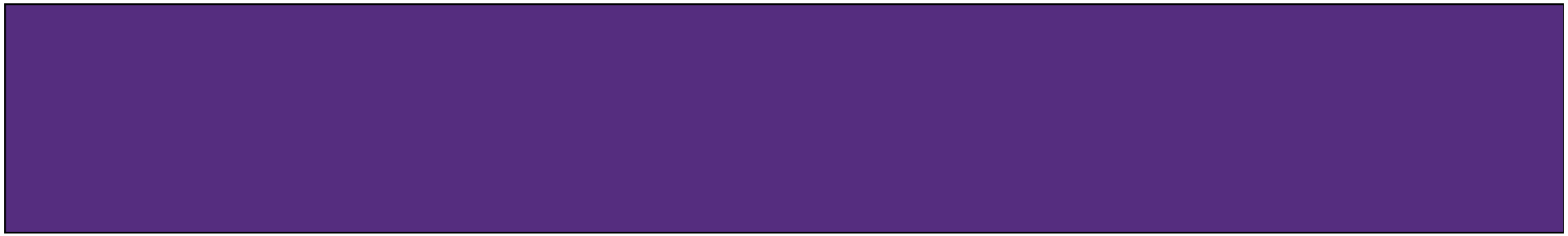
Time-averaged data; * $p<0.0001$

Effect of longer HD on premature ventricular ectopia



- Decrease in PVE at all time-points in the NHD group, no change in CHD patients

Dheir H et al, ASN Congress 2008



Patients with diabetes (n=160)

	HF	**LF**	p
Composite CV event-free survival (%)	82.3	67.5	0.05
Overall survival (%)	68.4	46.3	0.02
Cardiovascular survival (%)	86.1	68.8	0.01

- HF was associated with a 51% decrease in composite cardiovascular events (p=0.03)

(In Cox-regression analysis adjusted for age, gender, CVD history and time on dialysis).

❑ Better CV event-free, CV and overall survival with high flux use in diabetic patients

Patients with HD duration >3 years (n=399)

Ultrapure dialysate versus standard dialysate

	Relative risk	95% CI	p
Composite CV events	0.55	0.31-0.97	0.04

	UD	**SD**	p
hs-CRP (mg/dl)	1.34 ± 1.34	1.65 ± 1.66	0.03
Progression of CACs	303 ± 515	586 ± 48	0.03

- Lower CV event rate along with lower CRP levels by ultra-pure dialysate use in patients with HD duration over 3 years

Time-averaged laboratory values in the UD and the SD groups

- No difference in spKt/V, URR, PO4, albumin, Hb, lipids, CRP, β-2 microglobulin, and ferritin
- Dialysate endotoxin level decreased from 0.16±0.26 EU/ml to 0.01±0.01 EU/ml in the UD group ($p<0.001$), remained stable in the SD group (from 0.19 ± 0.34 EU/ml to 0.17 ± 0.35 EU/ml, $p=0.78$)

	UD (n=352)	**SD** (n=352)	**p**
Erythropoietin dose (IU/week)	**2213 ± 2006**	**2523 ± 2021**	**0.04**

❑ Reduction in Epo requirement with use of ultra-pure dialysate

CV event-free, overall and CV survival in HF and LF groups

	HF	LF	p
▪ **Fatal and non-fatal CV event-free survival**	87.5	83.0	0.12
RR with HF 0.73 (95%CI 0.49-1.08), p=0.12			

	HF	LF	p
▪ Overall survival (%)	78.7	72.4	0.09
▪ CV survival (%)	88.9	84.9	0.14

❑ A trend for better CV event-free, CV and overall survival in HF vs LF

CV event-free, overall and CV survival in dialysate groups

	UD	SD	p
▪ **Fatal and non-fatal CV event-free survival** (%)	85.5	84.9	0.67
RR with UD 0.90 (95%CI 0.61-1.32), p=0.60			

	UD	SD	p
▪ **CV survival** (%)	86.6	87.2	0.94
▪ **Overall survival** (%)	75.3	75.9	0.82

❑ No difference between UD and SD groups regarding CV event-free, CV and overall survival

Time-averaged laboratory values in the UD and the SD groups

- No difference in spKt/V, URR, PO4, albumin, Hb, lipids, CRP, β-2 microglobulin, and ferritin
- Dialysate endotoxin level decreased from 0.16±0.26 EU/ml to 0.01±0.01 EU/ml in the UD group ($p<0.001$), remained stable in the SD group (from 0.19 ± 0.34 EU/ml to 0.17 ± 0.35 EU/ml, $p=0.78$)

	UD (n=352)	**SD** (n=352)	**p**
Erythropoietin dose (IU/week)	**2213 ± 2006**	**2523 ± 2021**	**0.04**

❑ Reduction in Epo requirement with use of ultra-pure dialysate

- Inclusion criteria:
  - To be older than 18 years,
  - to be on maintenance bicarbonate HD scheduled thrice weekly 12 hours/week
  - willingness to participate in the study with a written informed consent
- Exclusion criteria:
  - to be scheduled for living donor renal transplantation,
  - to have serious life-limiting co-morbid situations, namely active malignancy, active infection, end-stage cardiac, pulmonary, or hepatic disease,
  - requirement for HD more than three times per week due to medical comorbid conditions,
  - mental incompetence
  - pregnancy or lactating

- **Sample size estimation**
- three-year duration of follow-up,
- annual rate of primary end-point to be 10%
- three year event-free survival of the control group 72.9% to detect an increase of 15% in event-free survival at the end of 3-year follow-up in favor of the each intervention group (90% power and a bilateral alpha risk equal to 5%)
- The required sample size: 704 patients (drop-out rate of 15-20%)

RESULTS

Baseline characteristics

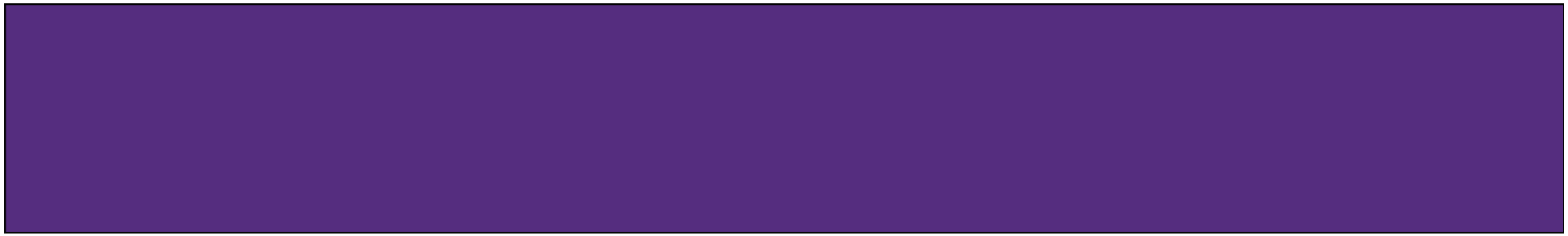
- Mean age 58.6±14.2 yrs, 46% female, diabetes 23%
- 82% had AV fistula
- In 95% of cases URR >65%
- SBP 125±16 mmHg, DBP 75±9 mmHg
- Patients on anti-hypertensive medication 7.9%

- Baseline clinical, demograhical, laboratory and medication characteristics were similar between dialyser and dialysate arms

Dialysis prescription

	HF arm n=352	LF arm n=352	UD arm n=352	SD arm n=352
Duration of sessions (min)	236 ± 4	236 ± 5	235 ± 5	236 ± 5
Blood flow rate (ml/min)	360 ± 32	359 ± 30	358 ± 31	361 ± 31
Dialyser	Helixone high-flux (Fx60 and Fx80) and synthetic low-flux (F7 HPS and F8 HPS) (FMC, Germany) No reuse			
Dialysate flow rate	500 ml/min			
Dialysate composition	Mostly Na 138 mmol/L, K 2.0 mmol/L, Ca 1.5 mmol/L			

Ultrapure dialysate: polysulfone-based filter (Diasafe, FMC Germany); change every three months; regularly check for CFU and endotoxin (LAL assay; Coatest Endotoxin Chromogenix, Mölndal, Sweden)



HE ol-HDF versus LE ol-HDF and HD
Multivariate analysis for cardiovascular mortality

	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
High-flux HD	Reference	Reference	Reference
HDF with RF ≤17.4 L	1.18 (0.72-1.94) p=0.50	1.27 (0.75-2.16) p=0.36	1.28 (0.75-2.19) p=0.35
HDF with RF > 17.4 L	**0.31** (0.14-0.65) p=0.002	**0.29** (0.13-0.65) p=0.003	**0.29** (0.12-0.65) p=0.003
Age (per year)		1.05 (1.03-1.08), p<0.001	1.05 (1.03-1.08) p<0.001
Presence of diabetes		2.03 (1.24-3.34) p=0.005	2.24 (1.35-3.73) p=0.002

Model 1: Adjusted with age, gender, diabetes, cardiovascular disease, time on hemodialysis, vascular access, blood flow rate and interdialytic weight gain

Model 2 – fully adjusted: Model 1+ hemoglobin, albumin, phosphate and urea reduction rate

OL-HDF → 71% RR REDUCTION IN CV MORTALITY

Follow-up

	OI-HDF	High-flux HD	p
Follow-up (months)	22.8 ± 10.6	22.6 ± 11.2	-
Duration of session (min)	236 ± 6	236 ± 11	0.75
Blood flow rate (ml/min)	318 ± 27	303 ± 32	<0.001

Mean substitution volume (L/session): **17.2 ± 1.2** (9.8-20.3);
>15L/s in 93% of patients

Endotoxin concentration (EU/ml): 0.005 ± 0.001; 94% undetectable

OL-HDF → HIGHER BLOOD FLOW RATE

Dialysis prescriptions

	Post-dilution OI-HDF*	HD
Dialyser	Fx series (Fx60 and Fx80), polisulfone, high-flux (FMC, Bad Homburg, Germany)	
Dialysis session	240 min X 3/week	
Blood flow rate	250 - 400 ml/min	
Dialysate composition	Na 138 mmol/L, K 2.0 mmol/L, Ca 1.5 mmol/L, Mg 0.5 mmol/L, HCO_3 32 mmol/L and glucose 5.5 mmol/L	

* ONLINEplus (FMC) integrated into Fresenius 4008S; two ultrafilters (DIASAFE plus), which were replaced after 100 treatments; **target substitution volume > 15 L/session**; dialysate and infusate regularly assessed for CFU and endotoxin level just before ultrafilter change (<0.1 CFU/mL; endotoxin level < 0.03 IU/mL)

Outcome Data

	All patients (n:782)	OI-HDF (n:391)	HD (n:391)	p
Primary Outcome*	**134 (9.04)**	**61 (8.19)**	**73 (9.89)**	**0.25**
Overall Mortality*	117 (7.89)	52 (6.98)	65 (8.80)	0.19
Cardiovascular Mortality *	76 (5.12)	32 (4.30)	44 (5.96)	0.40
Hospitalization rate*	290 (19.5)	152 (20.4)	138 (18.6)	0.44
Intradialytic hypotension**	79.4	77.7	81.0	0.64
Intradialytic cramp**	9.0	7.7	10.3	0.07

*** No of events (no/100- patient yrs of follow-up)**

**** Per 1000 session**

HIGH EFFICIENCY VS LOW EFFICIENCY oI-HDF

Baseline characteristics

	HD N=391	LE oI-HDF RF ≤ 17.4 L N=196	HE oI-HDF RF >17.4 L N=195	p
Substitution Volume		**16.2 ± 1.0**	**18.1 ± 0.68**	
Baseline parameters				
Age (years)	56.5 ± 14.9	56.9 ± 11.6	55.8 ± 13.8	0.69
Gender (F, %)	41	44	38	0.55
Time on HD (months)	58.7 ± 44.7	60.9 ± 45.8	53.6 ± 40.8	0.23
Diabetes (%)	33	42	32	0.02
CVD history (%)	25	25	29	0.63

MORE DIABETICS IN THE LOW EFFICIENCY OL-HDF GROUP

HIGH EFFICIENCY VS LOW EFFICIENCY oI-HDF
Baseline characteristics

	HD N=391	LE oI-HDF RF ≤ 17.4 L N=196	HE oI-HDF RF >17.4 L N=195	p
CVD history (%)	25	25	29	0.63
AV fistula (%)	95.4	95.4	97.5	0.24
Blood flow rate (ml/min)	294 ± 44	281 ± 38	304 ± 48	0.001
Systolic blood pressure	128 ± 16	128 ± 17	128 ± 15	0.90
Diastolic blood pressure	77 ± 8	77 ± 8	78 ± 7	0.57
Interdialytic weight gain (%)	3.47 ± 1.88	3.70 ± 1.57	3.40 ± 1.51	0.17

HIGHER BLOOD FLOW RATE IN THE HIGH EFFICIENCY OL-HDF GROUP

HIGH EFFICIENCY VS LOW EFFICIENCY oI-HDF
Baseline characteristics

	HD N=391	LE oI-HDF RF ≤ 17.4 L N= 196	HE oI-HDF RF >17.4 L N=195	p
Urea Reduction Rate (%)	74.5 ± 6.3	74.3 ± 7.3	75.6 ± 6.1	0.09
eKt/V	1.41 ± 0.25	1.39 ± 0.29	1.47 ± 0.26	0.09
Albumin (g/dl)	3.85 ± 0.38	3.75 ± 0.34	3.90 ± 0.33	<0.001
Hemoglobin (g/dl)	11.4 ± 1.44	11.7 ± 1.6	11.2 ± 1.41	0.002
Phosphate (mg/dl)	4.88 ± 1.48	5.13 ± 1.55	4.72 ± 1.29	0.01
CRP (mg/dl)	1.71 ± 2.36	1.85 ± 2.47	1.50 ± 2.08	0.30
Beta-2 microglobulin (mg/L)	26.1 ± 9.6	27.1 ± 7.9	25.7 ± 7.7	0.47

LOWER ALBUMIN, HIGHER HEMOGLOBIN AND PHOSPHATE IN THE LE OL-HDF

Primary Outcome

- **Composite of all-cause mortality and new non-fatal cardiovascular events** (myocardial infarction, stroke, revascularization, unstable angina pectoris requiring hospitalization)

Sample size estimation:

- two years follow-up,
- annual rate of primary outcome in CHD to be 20%,
- **35% decrease in risk of primary outcome by ol-HDF comparing to HD** (bilateral alpha risk equal to 5%; a 80% power to detect)
- 25% of annual dropout rate,
- The required sample was total 780 patients

Secondary Outcomes

- Cardiovascular mortality
- Hospitalization rate
- Intradialytic complications:
  - Hypotension episodes
  - Cramps
- Changes in:
  - Blood pressure
  - Post-dialysis body weight
  - Hb and related erythropoietin dose
  - Phosphorus
  - Albumin, lipids
  - High-sensitive C reactive protein (hsCRP)
  - β-2 microglobulin levels

STUDY DESIGN AND PATIENT SELECTION

- All patients (n: 1043) treated in 10 HD centers were screened
- After assessment of inclusion/exclusion criteria, 782 patients were randomized to ol-HDF and HD groups between Jan 2007 and March 2008
- Follow-up period was 24 months

- Inclusion criteria: >18 years old, 3 times weekly HD, spKt/V >1.2, written informed consent
- Exclusion criteria: Temporary catheter, blood flow rate 250 ml/min, urinary output >250 ml/d

Inclusion Criteria

- To be older than 18-years
- To be on thrice weekly 12 hours/week maintenance bicarbonate HD
- Have achieved mean single pool Kt/V above 1.2
- Willingness to participate in the study
- Give written informed consent

Exclusion Criteria

- To be scheduled for living donor renal transplantation
- To have serious life-limiting co-morbid situations namely active malignancy, active infection, end-stage cardiac, pulmonary, or hepatic disease
- Requirement for HD more than 3 times/week due to medical comorbidity
- Have temporary catheter as a vascular access
- Insufficient vascular access (blood flow rate<250 ml/min)
- Mental incompetence
- Pregnancy or lactation

Primary Outcome

- **Composite of all-cause mortality and new non-fatal cardiovascular events** (myocardial infarction, stroke, revascularization, unstable angina pectoris requiring hospitalization)

Sample size estimation:

- two years follow-up,
- annual rate of primary outcome in CHD to be 20%,
- **35% decrease in risk of primary outcome by ol-HDF comparing to HD** (bilateral alpha risk equal to 5%; a 80% power to detect)
- 25% of annual dropout rate,
- The required sample was total 780 patients

Baseline Data

	All patients (n=782)	On-line HDF (n=391)	High-flux HD (n=391)	p value
Vascular access (% AV fistula)	95.5	95.7	95.4	0.86
Blood flow rate (mL/min)	294 ± 45	294 ± 46	294 ± 44	0.94
Body mass index (kg/m^2)	24.8 ± 4.8	24.9 ± 4.9	24.8 ± 4.6	0.65
Post-dialytic body weight (kg)	67.9 ± 13.4	67.9 ± 13.5	67.9 ± 13.4	0.99
Systolic BP (mmHg)	128 ± 15	128 ± 15	127 ± 16	0.78
Diastolic BP (mmHg)	78 ± 8	78 ± 7	78 ± 8	0.64
IDWG (% of BW)	3.5 ± 1.7	3.5 ± 1.5	3.4 ± 1.8	0.70
Anti-HT medication (%)	13.6	13.1	14.2	0.82

HIGH AV FISTULA, ADEQUATE BP CONTROL, LOW ANTIHYPERTENSIVE USE

Baseline Data

	On-line HDF (n=391)	High-flux HD (n=391)	p value
Urea (mg/dl)	136 ± 34	134 ± 35	0.53
Creatinine (mg/dl)	8.0 ± 1.9	8.0 ± 2.3	0.84
Sodium (mEq/L)	136 ± 3	136 ± 3	0.84
Potassium (mEq/L)	5.11 ± 0.75	5.08 ± 0.797	0.60
Urea reduction rate (%)	74.9 ± 6.7	74.5 ± 6.3	0.46
eKt/V	1.44 ± 0.27	1.42 ± 0.25	0.29
Calcium (mg/dl)	8.66 ± 0.74	8.69 ± 0.67	0.50
Phosphate (mg/dl)	4.90 ± 1.42	4.88 ± 1.48	0.88
Ca-P product (mg^2/dl^2)	42.5 ± 13.3	42.6 ± 13.4	0.91
PTH (pg/ml)	370 ± 324	359 ± 328	0.66
Albumin (g/dl)	3.83 ± 0.35	3.85 ± 0.38	0.46

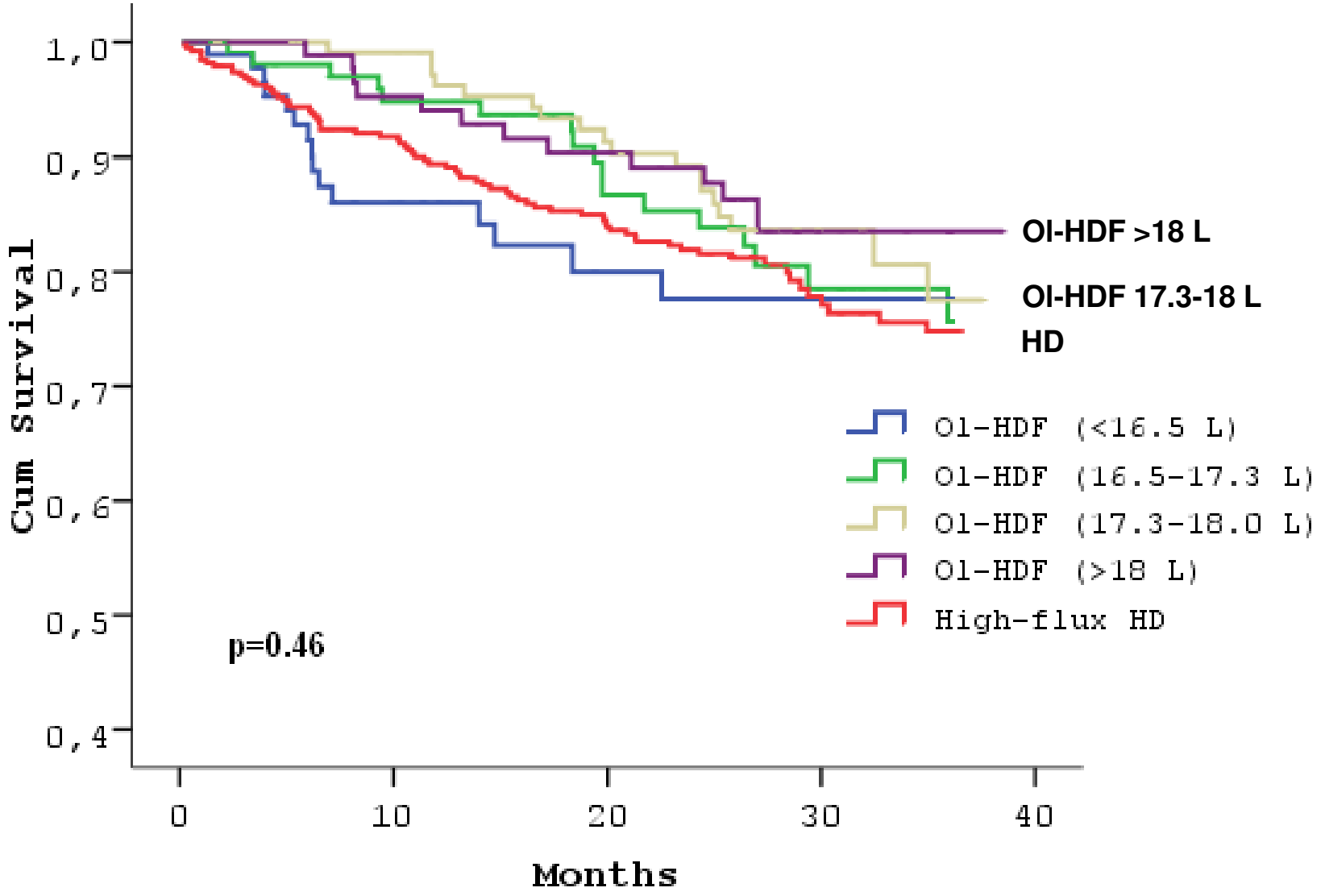
ADEQUATE DIALYSIS, ACCEPTABLE NUTRITIONAL AND MINERAL METABOLISM

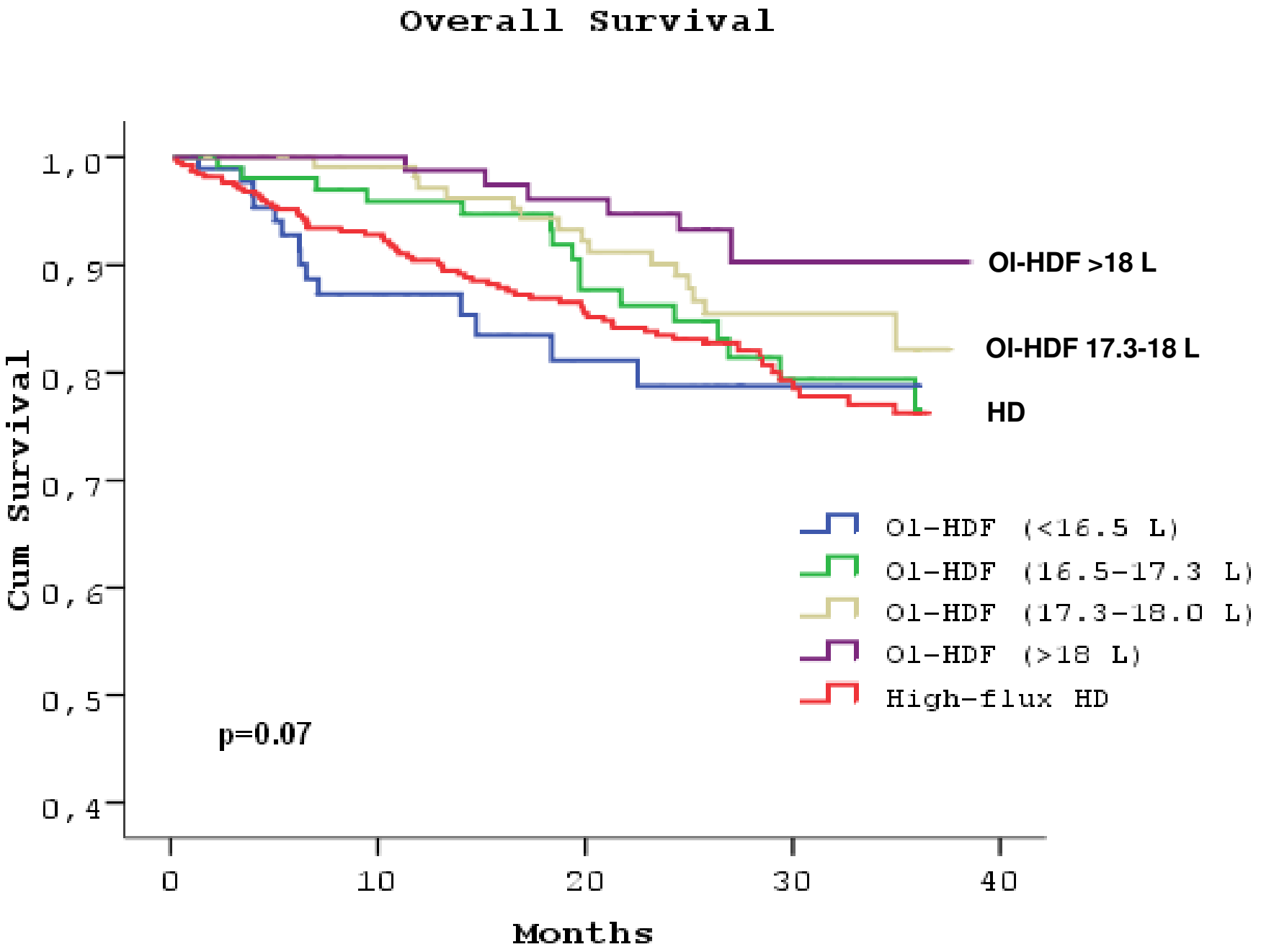
Baseline Data

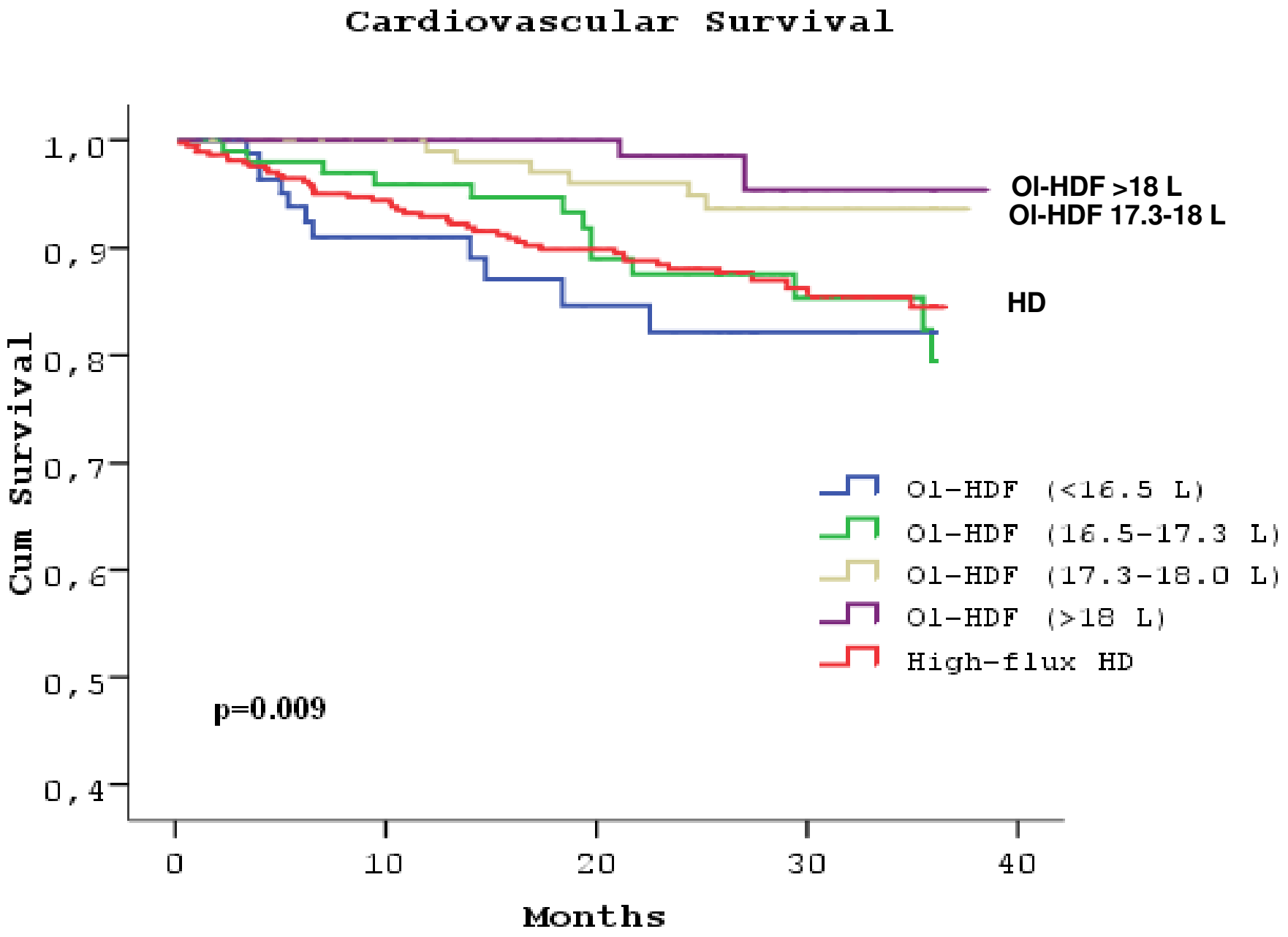
	On-line HDF (n=391)	High-flux HD (n=391)	p value
Total cholesterol (mg/dl)	173 ± 41	174 ± 43	0.61
Triglyceride (mg/dl)	179 ± 119	184 ± 109	0.59
HDL cholesterol (mg/dl)	43.9 ± 12.4	44.3 ± 12.0	0.66
LDL cholesterol (mg/dl)	93.1 ± 32.4	92.7 ± 31.6	0.87
Hemoglobin (g/dl)	11.4 ± 1.52	11.4 ± 1.44	0.85
Ferritin (ng/ml)	846 ± 644	816 ± 654	0.55
Transferrin saturation (%)	28.0	28.4	0.76
Bicarbonate (mEq/L)	22.7 ± 2.6	22.6 ± 2.5	0.73
Hs-CRP (mg/dl)	1.72 ± 2.38	1.71 ± 2.36	0.93
Beta-2 MG (mg/L)	26.5 ± 7.9	26.1 ± 9.7	0.57

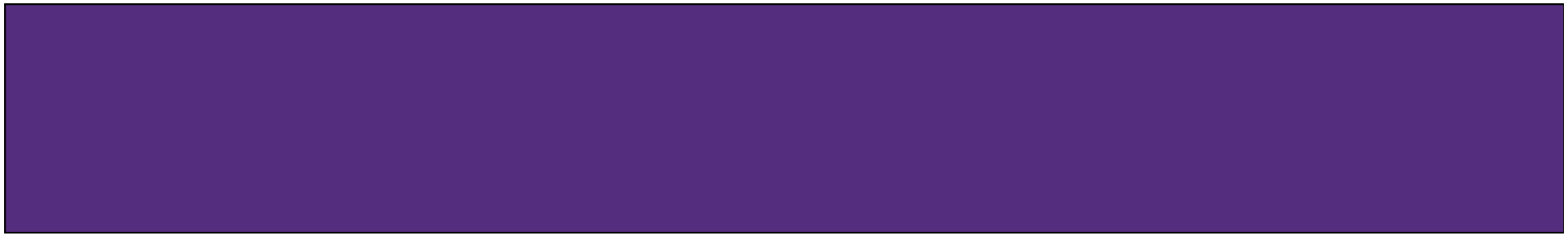
ADEQUATE ANEMIA CONTROL

Composite of fatal and nonfatal cardiovascular events-free survival

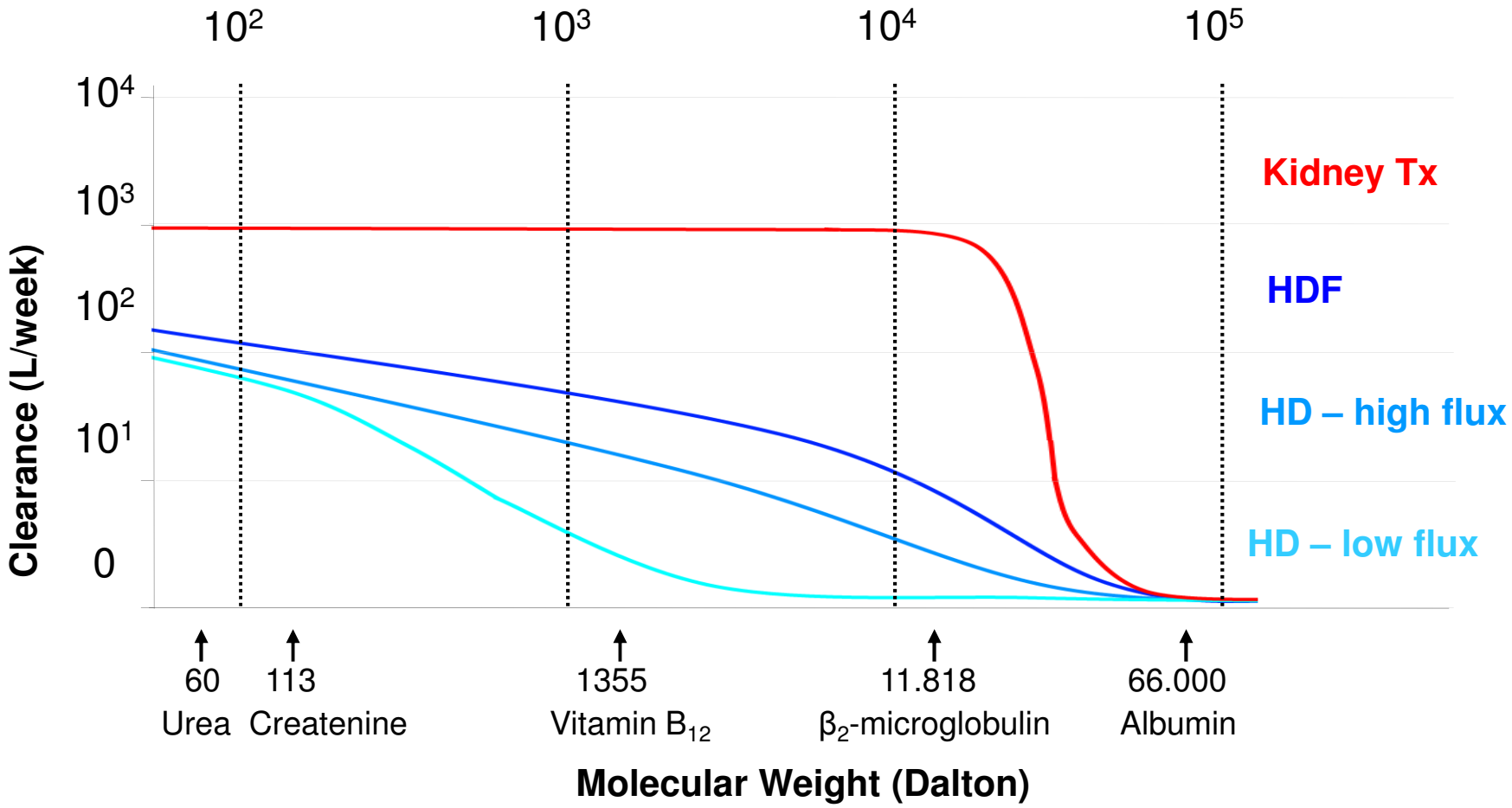



Overall Survival
Cum Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0
10
20
30
40
Months
p=0.07
Ol-HDF >18 L
Ol-HDF 17.3-18 L
HD
Ol-HDF (<16.5 L)
Ol-HDF (16.5-17.3 L)
Ol-HDF (17.3-18.0 L)
Ol-HDF (>18 L)
High-flux HD

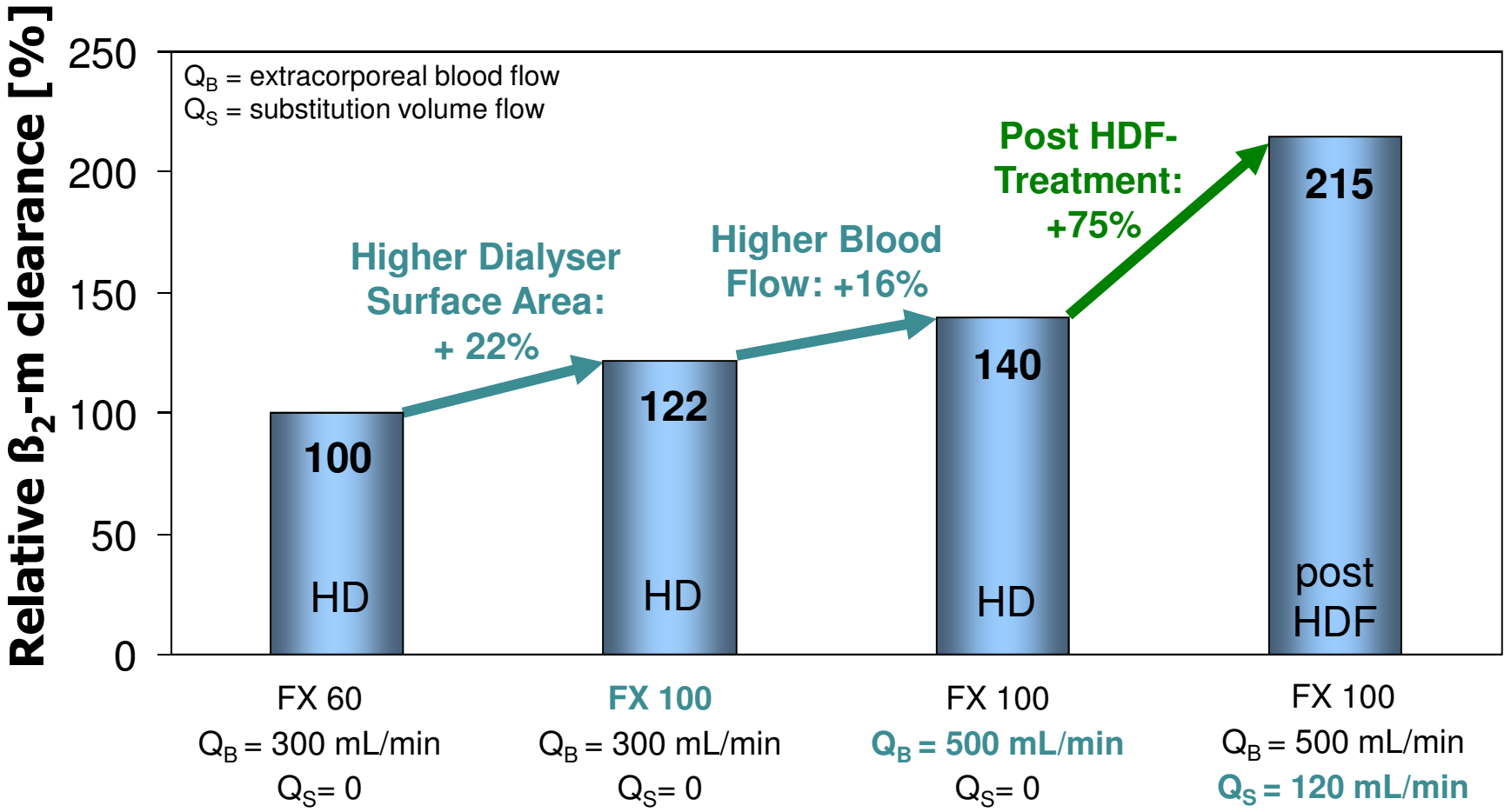

Cardiovascular Survival
Cum Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0
10
20
30
40
Months
p=0.009
Ol-HDF >18 L
Ol-HDF 17.3-18 L
HD
Ol-HDF (<16.5 L)
Ol-HDF (16.5-17.3 L)
Ol-HDF (17.3-18.0 L)
Ol-HDF (>18 L)
High-flux HD



Comparing Renal Replacement Therapies



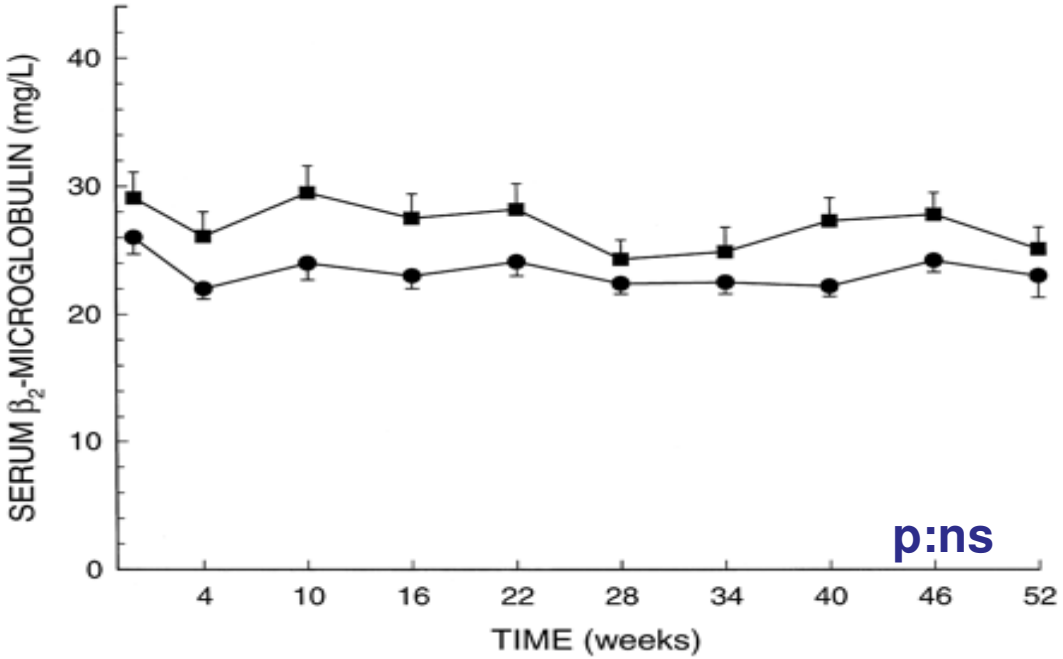
Convection is essential for Middle-Molecule Removal



Wizemann et al. Nephrol Dial Transplant 2001; 16 (Suppl 4): 21-30

Predialysis β-2 microglobulin levels in HDF and HD

- Online HDF vs high-flux HD
- PRC study
- Pre dialysis β-2 microglobulin levels

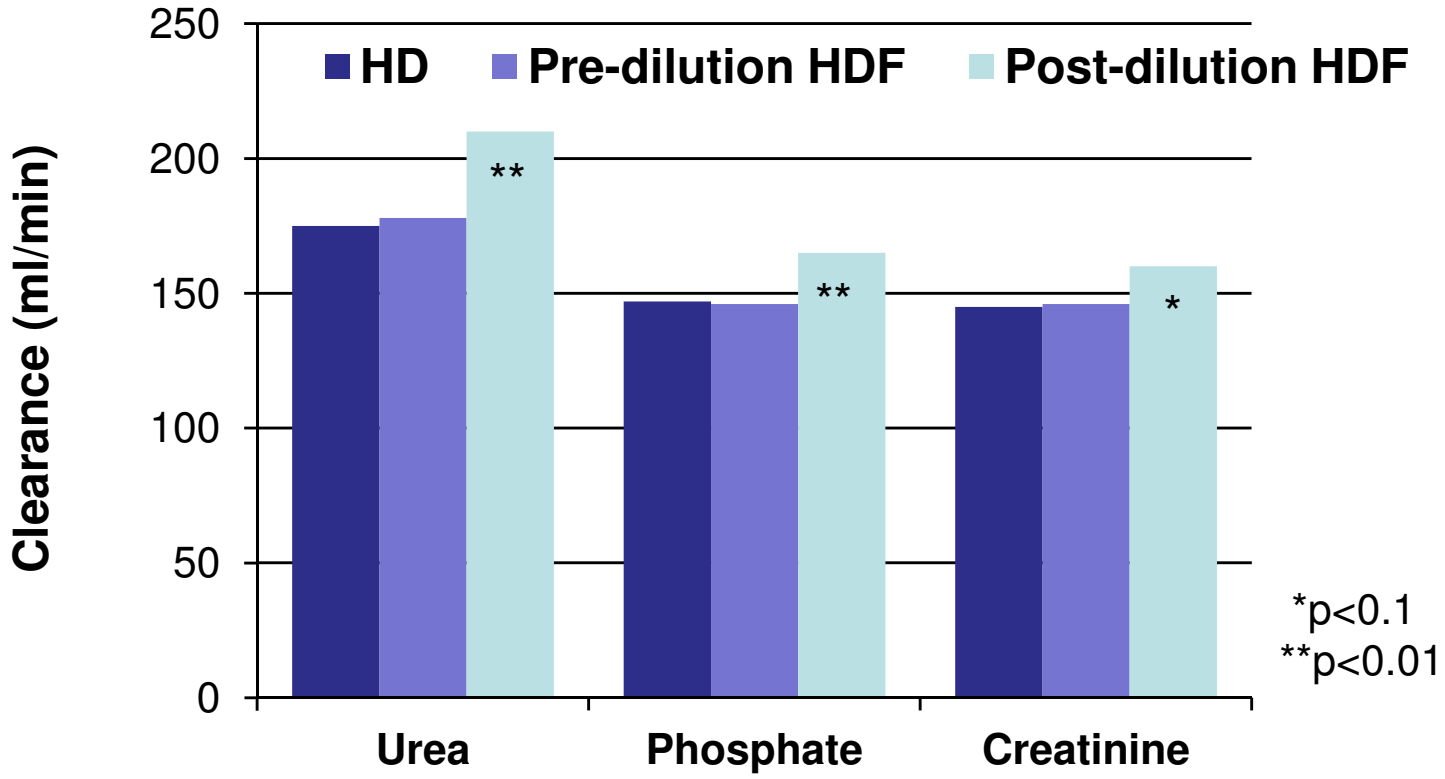


Ward RA. J Am Soc Nephrol 2000;11:2344-50

- Predialysis β-2 microglobulin levels not different in HDF and HD
- Slow intercompartmental transfer of β-2 microglobulin

Ward RA. Kidney Int 2006;69:1431

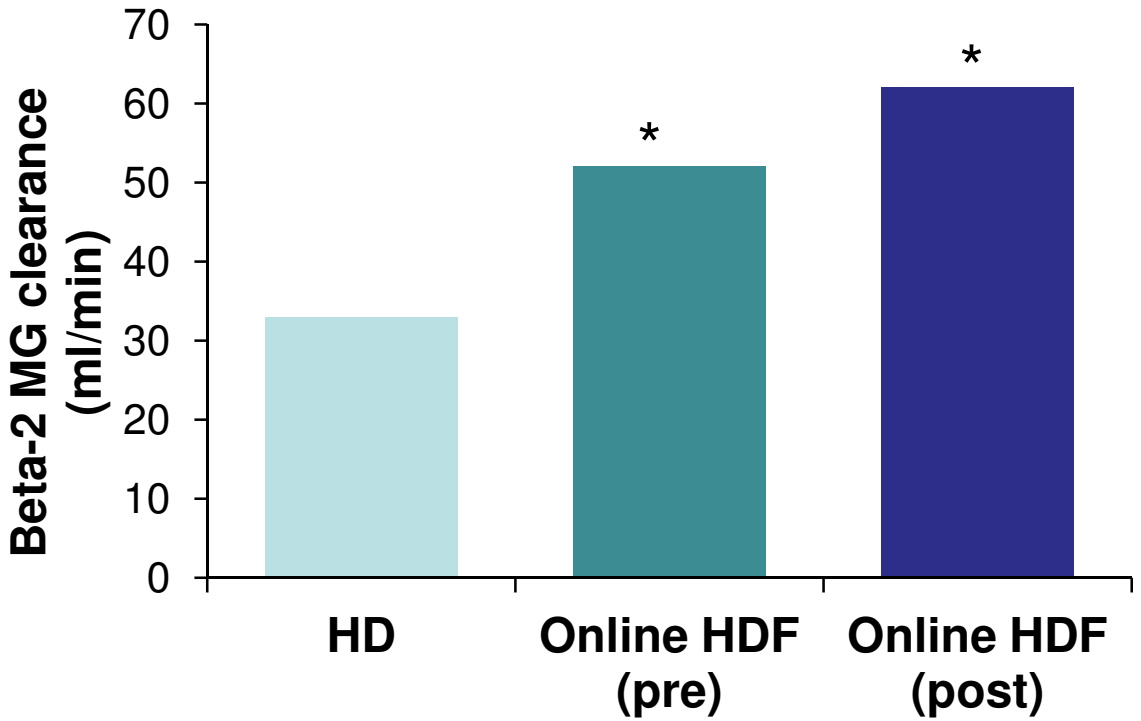
HDF and solute clearance



Ahrenholz P et al, Int J Artif Organs 1997

- **Higher urea, creatinine and phosphate clearance with post-dilution ol-HDF**

β-2 microglobulin clearance with HDF

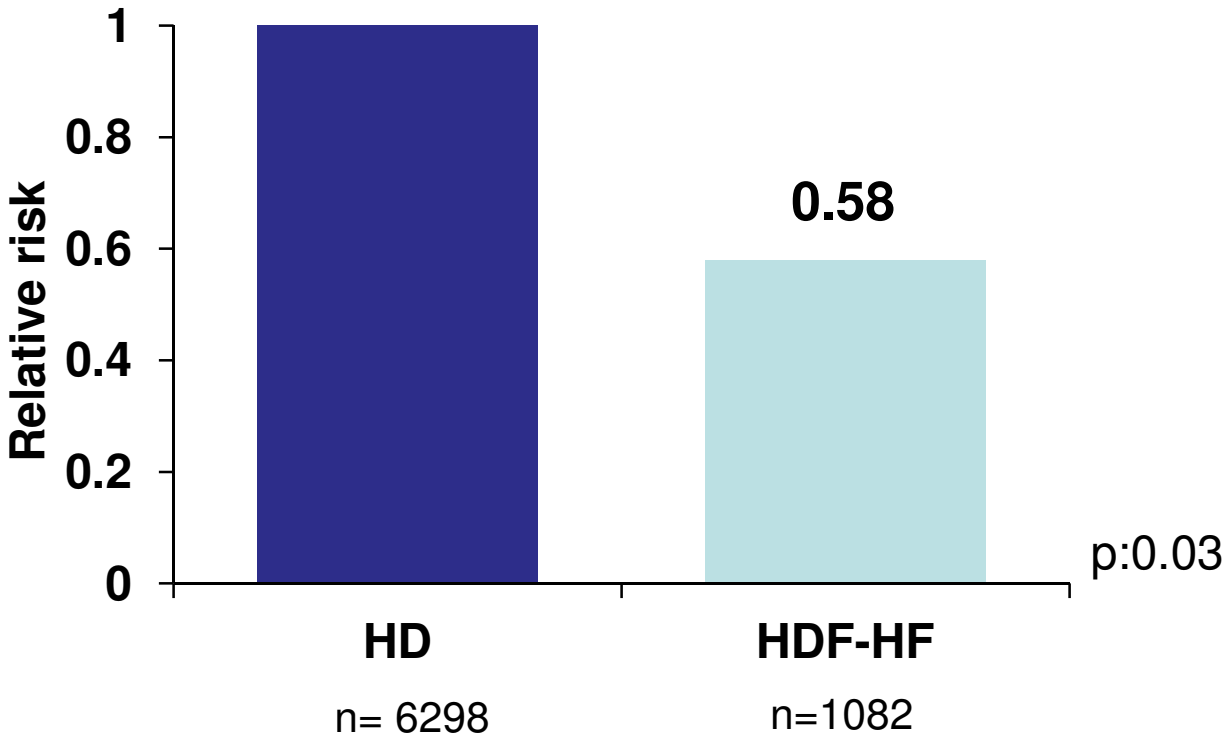


*p<0.001

Ahrenholz P, et al, Int J Artif Organs 1997

➢ **β-2 microglobulin clearance: post-dilution HDF > pre-dilution HDF > HD**

HDF and carpal-tunnel syndrome

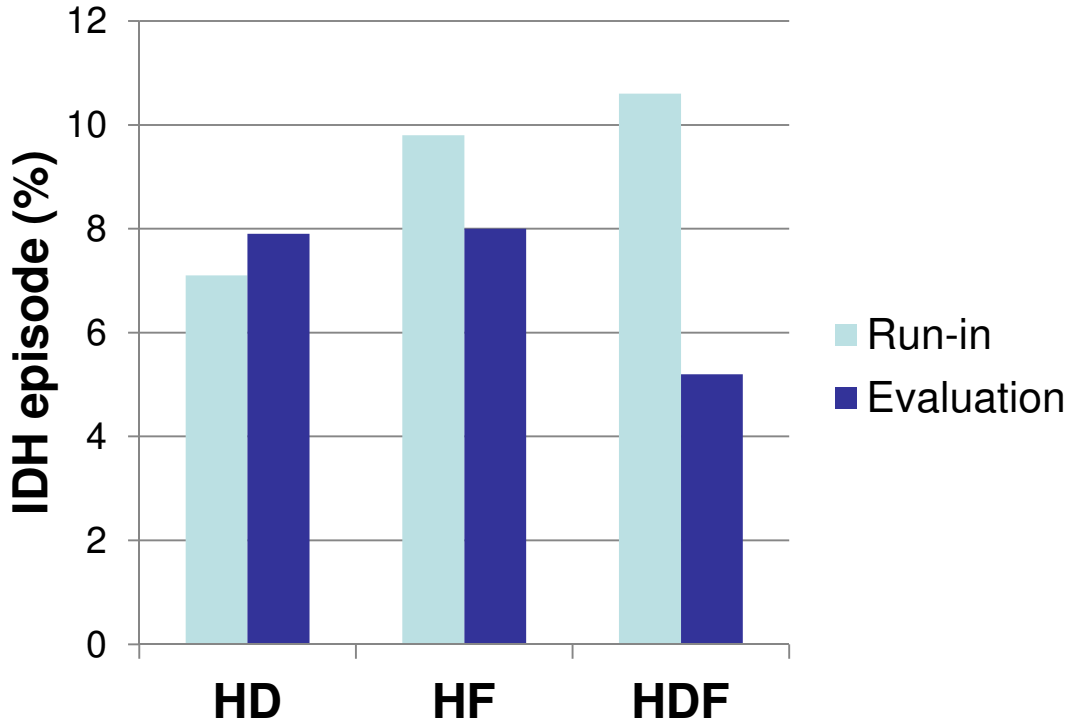


Locatelli F, et al Kidney Int 1999

- **Frequency of carpal tunnel syndrome 42% less in patients treated with HDF**

Hemodinamic stability with on-line HDF

- LF-HD, HF and pre-dilution ol-HDF (246 pts in each arm)
- PRC study, 2 year follow-up



Locatelli F, J Am Soc Nephrol 2010

➢ **Reduction in intradialytic hypotension episodes with pre-dilution ol-HDF**